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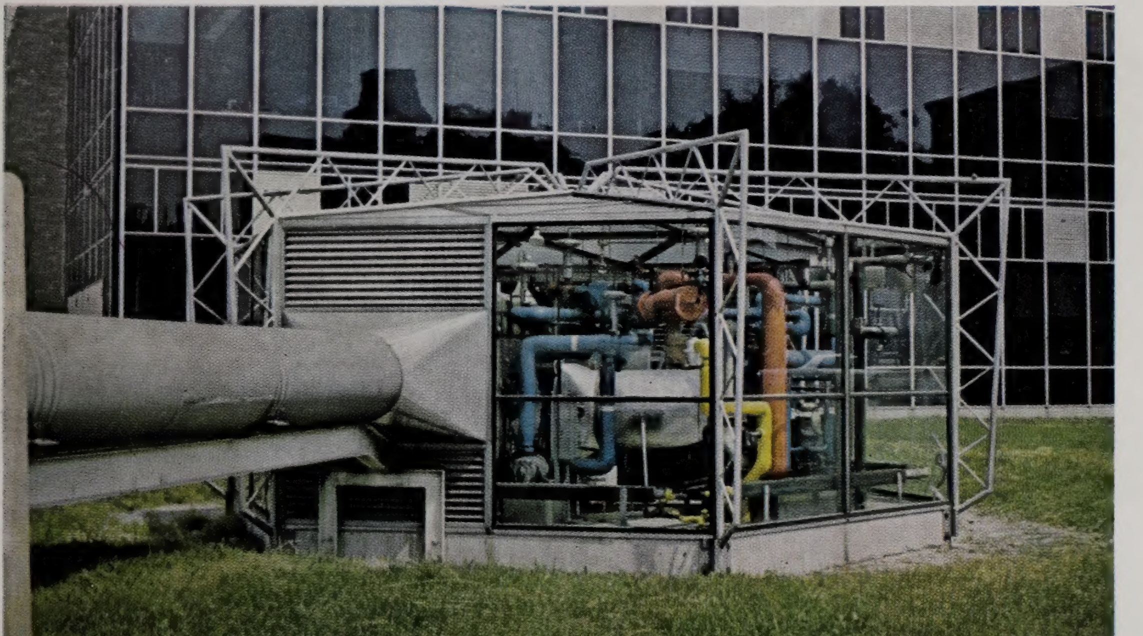

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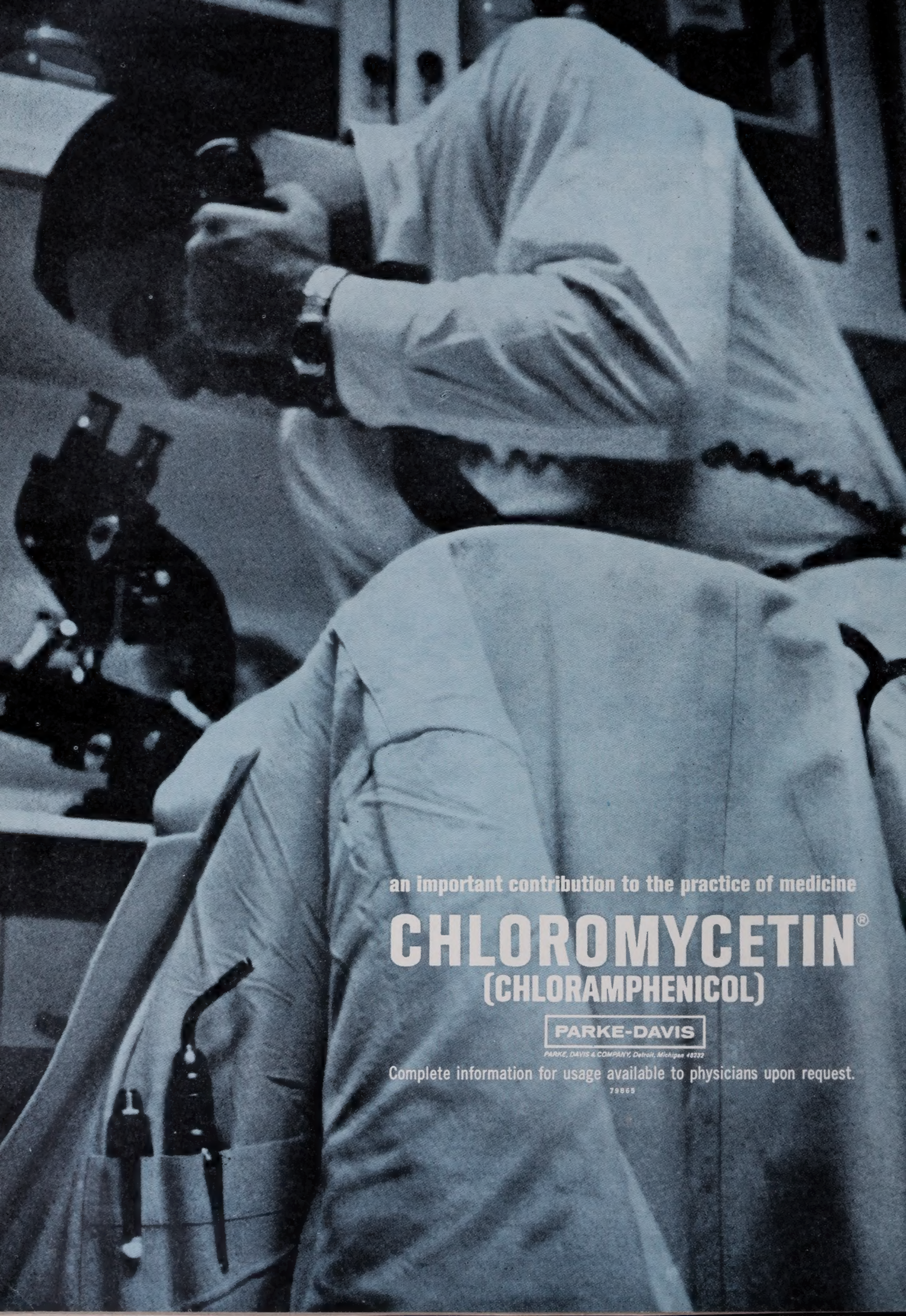

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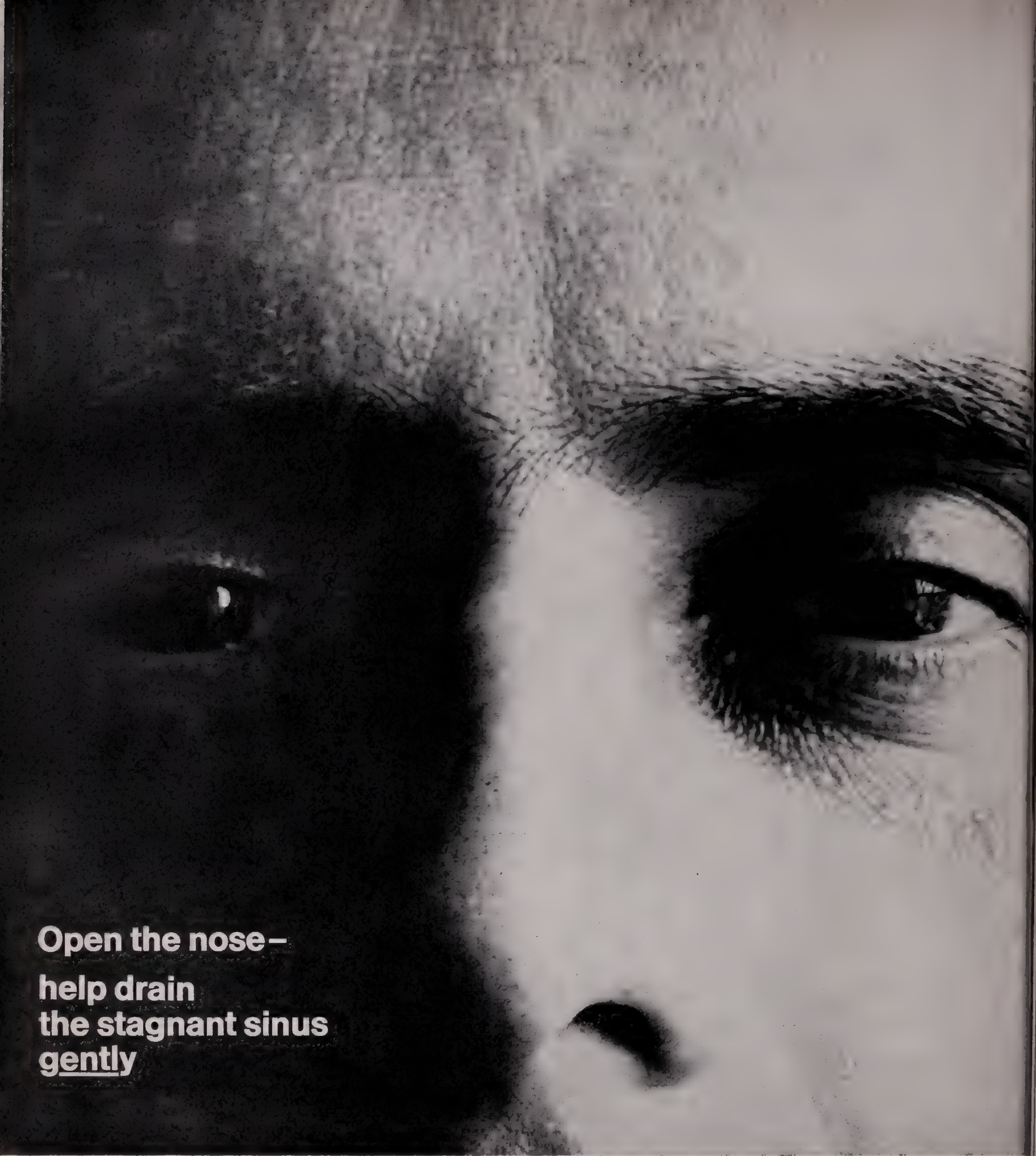

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President's Letter

To be elected President of the Minnesota State Medical Association is a great honor, one to be accepted with humility, for the office carries with it many responsibilities. The development of the scientific program for the following year, certain committee appointments, attendance at multiple meetings and functions are part of the President's obligations, but are of less significance than the major responsibility: that of spokesman for the Association.

All of us realize that medicine is at a crossroad, and that the choice of direction is no longer entirely ours. We can, hopefully, indicate in the future what path we prefer, but our choice will depend in large part on the unified resistance we present to misdirection.

Since the President is identified as the spokesman for Association policy and principle, he must be alert to and aware of Association attitudes, in order that he be prepared to explain, and, if necessary, defend these attitudes.

Through county society delegate election, and subsequent House of Delegate reference committee hearings and recommendations to the House, every member has a choice in determining Association policy. The Council in the interim between sessions of the House further clarifies Association policy and the principles on which Association actions are based.

These procedures in the House and in the Council structure are the official method to fully present, and represent the thinking of the physicians of Minnesota.

Occasionally, it is true, individual physician opinion may not coincide with Association action. In areas as controversial as the future response of medicine to governmental regulation, some difference of opinion inevitably occurs. The actions of the Association are, however, always the distillate of elected representative opinion and should be accepted as such.

Varying opinions can, and should, be expressed in component society meetings, before reference committees, before the House of Delegates itself, and by way of the always open door to Council deliberations.

Never in the past has a united front been so necessary to medicine, for never in the past have physician statements been so suspect and so freely criticized.

This is in no sense a plea for conformity, for conformity alone leads to compulsion, and agreement without honest discussion of issues leads to complacency. It is, rather, a plea for individual physician participation in the formation of Association policy through active component society attendance, through delegate instruction, through attendance at the annual meetings, at the House of Delegates, and at the reference committees which shape policy for recommendation to the House.

By this participation, the physicians of Minnesota can clearly express medical policy, motivation and philosophy, individually and as members of a stronger Association.

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Aneurysmal Abscess*

HUBERT C. HUEBL, M.D.****
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Detroit, Michigan

ALTHOUGH INFECTION is an unusual cause of aneurysm, we have recently encountered four cases which resulted from arterial injection. Two followed carotid arteriography; the others occurred in addicts who had been introducing concentrated paregoric mixtures into their femoral veins. In each instance the lesion presented as a pulsating abscess and was treated by ligature, incision, and wide drainage.

It is our purpose to document this experience and to describe the relative importance of extravasation, contamination, intramural injection, and chemical necrosis in its etiology. In addition, the question of immediate or delayed vascular reconstruction will be discussed.

Case Reports

Case #1

A 53-year-old negro male was admitted to Detroit Receiving Hospital on January 4, 1964, because of the onset of headache associated with tingling, decreased sensation, and weakness in his left upper and lower extremities. On physical examination his blood pressure was 170/110. He was obtunded† and poorly oriented, but responded to simple commands. Speech was slurred. He was noted to have a left facial paresis and a left hemiparesis and hypesthesia. Deep tendon reflexes were diminished on the left. There was slight nuchal resistance. Initial laboratory studies were within normal limits. Lumbar puncture revealed an opening pressure of 370 mm. of saline and a closing pressure of 300. The fluid was bloody. Protein was 420 mgm%.

Diagnostic Procedure

On the day following admission, bilateral carotid arteriograms were performed using Renografin 60. This revealed marked tortuosity and kinking of the internal carotid arteries and cerebral vessels, especially on the right. No other abnormalities were seen. He was noted to have extravasation of dye into the right carotid sheath, which was controlled with pressure. Bilateral brachial-vertebral arteriograms showed no pathology in the subclavian or vertebral vessels.

He began to improve, but on the seventh day following arteriography he was observed to have a pulsating, tender mass involving the entire right side of his neck from the occiput to the sternum, associated with a Horner's syndrome. The mass was reported to have appeared during the preceding twenty-four hours and was rapidly expanding. His temperature rose to 104° and his pulse increased to 130. A tracheotomy was performed by the Eye, Nose and Throat service because the trachea was shifted to the left and he had pressure symptoms from the mass.

Operative Findings

The right side of the neck was explored. There was a considerable amount of inflammation with seepage of purulent material as the layers were dissected. When the carotid sheath was approached, aneurysmal dilatation was apparent, and it was decided to obtain proximal control of the carotid artery at the base of the neck. As this dissection was begun, spontaneous rupture occurred, resulting in severe hemorrhage which was arrested with pressure. The common carotid artery was isolated in a lesser involved segment just above the sternum and occluded with umbilical tape. The vessel was exposed in the infected area and found to be inflamed, necrotic, and very friable for a distance of several centimeters, with a defect which communicated with the aneurysmal space. It was considered impossible to repair this defect, nor was it thought advisable to utilize a graft. Accordingly, proximal and distal ligation was carried out. At the distal end, which was at the bifurcation, it was necessary to take large suture ligatures including surrounding tissues. Because the wound was large and gaping, Penrose

---

*Supported by NIH Grant AM 06385-03, Michigan Heart Association and Receiving Hospital Research Corporation.

**From the Robert S. Marx Laboratories of the Department of Surgery, Wayne State University, School of Medicine, Detroit, Michigan.

†See Test Your Word Score Page 97.

drains were placed in the depth and it was partly approximated with silk sutures in the skin.

Pathologic Findings

Blood cultures were negative. Cultures of the wound grew out Staphylococcus aureus coagulase positive, Staphylococcus albus coagulase negative, and alpha streptococcus. The patient was treated with penicillin, streptomycin, chloromycetin, and later Staphcillin. Local wound care included hydrogen peroxide irrigations. He appeared to be improving; but two weeks later during a dressing change he began to bleed profusely from the distal end of the carotid artery, and on repeated exploration he was found to have additional necrosis of the vessels, requiring higher ligation of the internal and external carotid artery. He subsequently had a septic course with spiking temperatures of 104° and expired. At autopsy he was found to have interstitial pneumonia and septic changes in multiple organs. He had chronic pyelonephritis and generalized arteriosclerosis with massive infarction of the right cerebral hemisphere.

Case #2

A 74-year-old white male was admitted with a three-day history of headache, difficulty with speech, and weakness of his right upper and lower extremities. He was somewhat drowsy and confused. In 1949 he had had an abdomino-perineal resection for carcinoma of the rectum, at which time he also reportedly had a right nephrectomy and partial hepatectomy.

Physical Findings

Physical examination revealed a blood pressure of 165/115. Examination of the lungs and heart was within normal limits. There were incisional scars in the abdomen and a colostomy on the left. There was no nuchal rigidity, facial asymmetry, or motor impairment. He had a depressed corneal reflex, and the uvula deviated to the right. On the right side, he also had facial hypesthesia and hemiparesis, with decreased deep tendon reflexes.

Laboratory Studies

Basic laboratory studies were normal. Lumbar

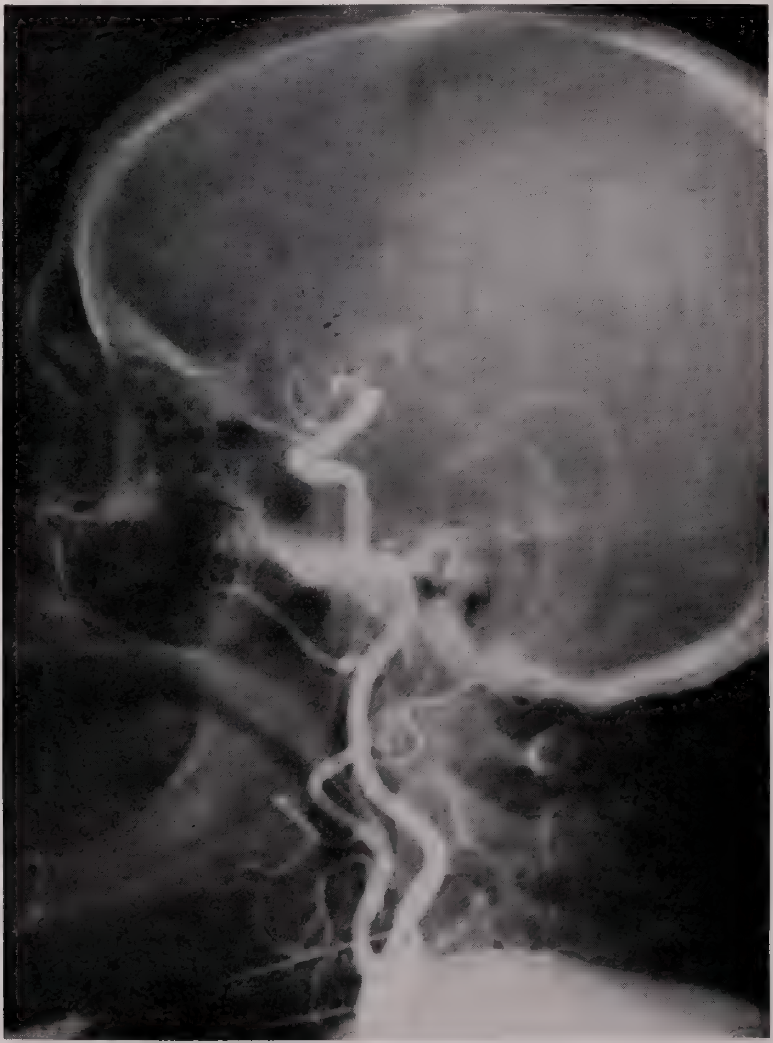

Fig. 1 — A roentgenogram taken at the time of the diagnostic carotid arteriography revealing injection of the left carotid sheath in Case 2.

puncture was done with an opening pressure of 120 mm. of saline and a closing pressure of 110. The fluid was bloody with a protein of 98 mgm% and a sugar of 50 mgm%. Skull films were normal. On chest x-ray, he was found to have cardiomegaly and a right pleural effusion. Electroencephalography was compatible with a subcortical lesion in the left hemisphere. Bilateral carotid arteriograms were done on February 6, using Renografin 60, with no abnormalities visible. However, injection of the carotid sheath was noted on the left (Figure 1).

Operative Findings

Eight days later he was noted to have a large tender mass involving most of the left side of the neck and a temperature of 101°. As a result of our previous experience, the possibility of an aneurysmal abscess was considered. The neck was explored and at the start of the procedure the carotid artery was exposed and controlled with umbilical tape at its emergence into the neck. Distally, the internal and external carotid arteries were similarly isolated. As the incision was carried into the mass, necrotic, purulent exudate escaped from the wound edges. A large excavation was encountered which communicated with an opening in the common carotid artery, a long segment of which was necrotic and friable and could not be preserved. The infection invaded extensively into the surrounding area with alteration of the tissues. Proximal and distal ligature of the carotid artery was accomplished. The wound was allowed to remain wide open, and the patient was treated with local dressings, irrigations, and systemic antibiotics. Postoperative neurologic examination was unchanged. In a few days a clean, granulating base developed and subsequently closed rapidly. There was no problem with additional bleeding. He was discharged after four weeks, to be followed in the Out-Patient Department.

Case #3

A 41-year-old negro male narcotics addict had been injecting paregoric into his femoral veins. He was admitted June 12, 1964, with a mass in his right groin which had been enlarging progressively for two weeks. There were multiple puncture scars in the extremities. Physical examination indicated a blood pressure of 120/60.

Physical Examination

Examination of the heart, lungs, and abdomen was within normal limits. There was a tender, indurated, pulsatile mass in the right femoral area extending from the inguinal ligament to the midthigh. Basic laboratory studies were normal, except for a white count of 18,000.

Operative Findings

On exploration, he was found to have extensive purulent inflammatory reaction in the tissues of the iliofemoral area. The entire upper thigh in its anteromedial aspect was indurated, edematous and

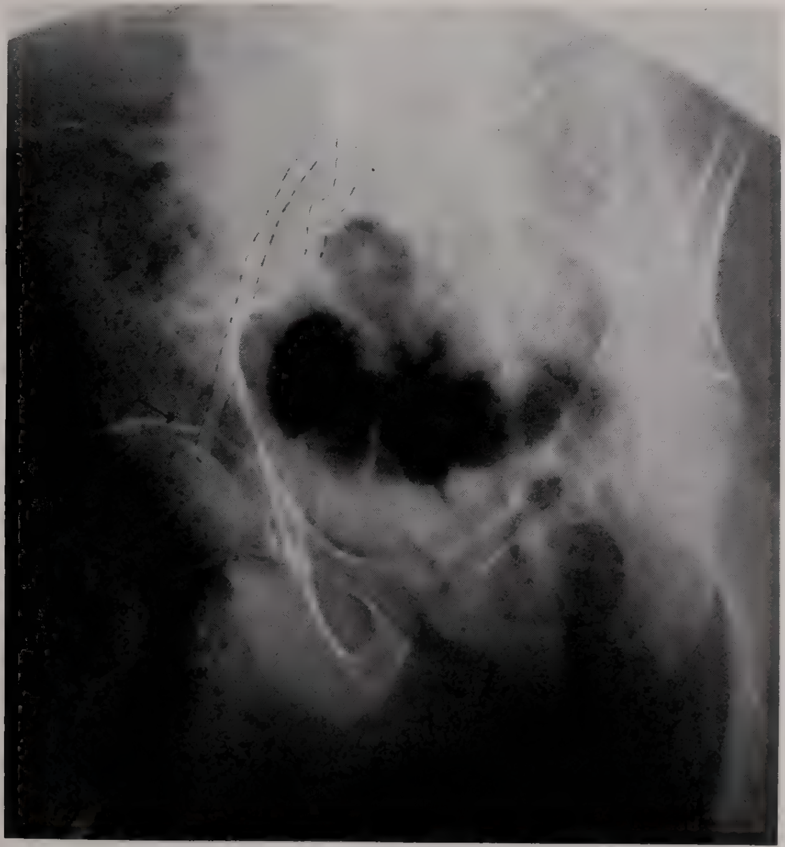

Fig. 2 — This x-ray was obtained following the initial surgical procedure. It shows termination of the dye column at the external iliac artery on the involved side. (Case 3)

tender. In this instance, prior arterial control was not obtained, and a large, infected, blood-filled space in communication with the femoral artery was entered, producing brisk hemorrhage. It was necessary to ligate the femoral artery above and below the site and to tie off the profunda femoris as well, leaving a defect in the vessel several centimeters in length. He was able to maintain circulation and viability in the extremity and the wound was healing satisfactorily on discharge from the hospital.

A reconstructive procedure was planned. However, this man went elsewhere. Figure 2 shows the arteriogram obtained in that hospital. A bypass graft was inserted which subsequently clotted. He is being followed currently by this surgeon.

Case #4

This patient was a 34-year-old negro male with a twenty-year history of drug addiction. He was admitted with a large, tender, painful mass in his right groin which had been present for one week. The history was otherwise not contributory. On physical examination, his blood pressure was 140/90, temperature 101°, pulse 110. Examination of the heart, lungs and abdomen was unremarkable. Laboratory studies were within normal limits.

Operative Finding

On exploration he was found to have a hematoma beneath the external oblique muscle just superior to the inguinal ligament. This collection extended deep into the ligament, and on the removal of the blood clots, arterial bleeding ensued, which was controlled with pressure. The incision was enlarged, and the iliac and femoral arteries were exposed and occluded proximally with an arterial clamp. Distally the vessel did not bleed. On removal of the remainder of the hematoma, the external iliac artery was found to be necrotic and destroyed for a distance of 5 cm. The artery was ligated where it had been entered. Drains were placed in the wound and the fascia loosely approximated.

Culture revealed the presence of aerobacter aerogenes, gamma streptococcus, Staphylococcus albus coagulase negative, and pseudomonas. His postoperative course was satisfactory under treatment with antibiotic and local care. He has since been lost to follow-up.

Discussion

The term "mycotic" was first used by Osler in 1885 to denote those aneurysms which result from septic emboli originating in vegetations of bacterial endocarditis.[5,7,10,12,15] Infection reaches the vessel wall either via the lumen or through the vasa vasorum.[4,13,14] Local sepsis can also affect the arterial wall either by lymphatic spread or more directly from an adjacent infective process.[3,4,13,14] The cases we have presented must be considered examples of this latter category.

Error in Technique

There seems little question that in our patients infection was introduced by means of contaminated instruments or materials, and that it played a major role in the disease process. Certainly this is not surprising where addicts are injecting themselves with opiates. However, the two cases in which infected aneurysm followed angiography are rare complications of this procedure and must be ascribed to a major break in technique.

Chemical Necrosis

Any contamination under these circumstances is augmented by the additional factor of chemical necrosis. When *contrast material* used in arteriography escapes into the vessel wall or into the surrounding area, it is known to be irritating and may result in necrosis and a corresponding inflammatory reaction, regardless of any superadded infection.[11] Similarly, in the addicts who were injecting concentrated paregoric, we surmise that the substance was inadvertently deposited into tissues near major vessels, or perhaps into the arterial wall itself. One of the ingredients is *camphor,* which has been used to produce necrotizing abscess in experimental animals. The resulting dead tissue offers little local defense against the spread of infection and may provide a good culture medium. Contaminating organisms can thrive not only on dead tissue, but also on extravasated blood. Some degree of extravasation must be expected with intravascular injection, but presumably it is greater if for some reason the arterial wall is torn. In one of these cases we do have evidence of intramural injection. Injury could occur either from the needle itself, from introduction of chemicals into the wall, or by the force of intramural injection.

Extravasated Blood

Extravasation of blood opens up a space for infection and in itself may cause some degree of necrosis of tissue. In this connection, one must consider the possibility that the infection was preceded by the development of a false aneurysm which results from arterial injury and has been reported to occur on rare occasions as a complication of percutaneous arteriography.[9,11,16] However, a false aneurysm is contained by a wall formed by compressed tissues in which there is organization.[5,6] In the cases we have reported, no such structure was recognized. It may well be that the time interval between the injection and the onset of these abscesses was too short for organization to occur. There is some question whether it is possible for organization to take place in a fulminating infection of this kind in which spreading factors and various enzymes may be released which can effect further tissue breakdown. These lesions appeared to be most closely akin to infected pulsating hematomas in which encapsulation is lacking.[5,8]

Treatment

Confronted with a rapidly enlarging mass with evidence not only of local sepsis, but also of generalized toxicity, drainage is the method of choice. The problem of differentiating between an abscess and an infected aneurysm may arise, as is illustrated by two of our cases. Others have reported similar difficulty.[1,5,17] We see a number of examples of abscess and thrombophlebitis in addicts. The presence of infection in the mass causes the entire area to be indurated so that the expansile nature of pulsations may not be appreciated.

Our experience suggests that the widest possible drainage is indicated in these lesions. Proximal and distal ligature of the vessels involved may be necessary to prevent exsanguination. Modern techniques would prompt one to try immediate reconstruction. In certain circumstances when critical arteries are involved, Smith, Szilagyi, Colville and others have practiced the use of autogenous vein grafts tunneled through uninfected tissue joining healthy artery above and below the defect.[14] The cases reported by these authors were localized lesions arising as embolic phenomena from sepsis elsewhere. Yet even in such cases where the pathologic process was relatively confined, grafting procedures in the involved areas often have been unsuccessful. We also have had some experience with mycotic aneurysms secondary to septic embolization in which there is a definite capsular structure. These usually have been of a more chronic duration — occasionally several months or years. Here both ligation of the artery and reconstruction with a venous graft have been employed to advantage. In our present series of cases, however, we were not dealing with lesions which were fairly well localized, as in true mycotic aneurysms. We were faced, rather, with such extensive tissue destruction and inflammation that it was thought unwise to place a graft in the vicinity.

It is interesting to note that in these patients ligature of major vessels did not result in gangrene. The addicts were young individuals and in addition may have developed sufficient collateral circulation as the aneurysm progressed. The two men who had difficulty following carotid angiography were orginally admitted with ischemic problems and may have previously developed collateral circulation.[2] In these instances, also, the original arteriosclerotic obstruction was on the same side as the subsequent infectious process.

Summary

Four cases are presented of infected aneurysms involving carotid and femoral arteries, which followed administration of angiographic media or, in addicts, concentrated paregoric mixtures.

We believe the lesions we have encountered resulted from a combination of infection, chemical necrosis, and extravasation of blood.

Treatment of these lesions involves incision, ligation, and wide drainage.

This entity differs from mycotic aneurysm in that the process is much more acute, and the patient presents with all the signs of an abscess. Vascular reconstruction was not deemed feasible.

Addendum

Two other patients with lesions similar to that described above were recently admitted to the surgical service. A 50-year-old diabetic was hospitalized elsewhere, August 30, 1965, with left hemiparesis and evidence of brain stem ischemia. Arteriograms revealed narrowing of both internal carotid arteries and of the left vertebral artery. On September 15, 1965, an endarterectomy was performed on the left common and internal carotid arteries, using a polyethylene bypass. The arteriotomy was closed primarily with 6-0 Tefdek.

Five weeks later she presented for the first time to our hospital, febrile, with an inflamed, expanding, pulsatile mass in the left side of her neck deep to the healed incision. There was blackening of the skin adjacent to the scar with frank gangrene of its lower end. Her breathing was impaired due to tracheal compression. The diagnosis of an aneurysmal abscess was made, and rupture was considered to be imminent. The patient was taken immediately to the operating room and a supraclavicular incision made, through which it was possible to obtain control of the carotid artery without entering the abscess. The mass was then incised and a foul-smelling blood clot was evacuated, revealing an aneurysmal abscess, identical in many respects to those we have described. There was extensive necrosis of the common carotid artery at its bifurcation, the site of previous surgery, with a hole in the vessel wall surrounded by brownish debris. Brisk arterial back bleeding arose from the internal and external carotid arteries. It was necessary to ligate them and the common carotid arteries at sites where the vessel would hold a suture. The wound was packed. Postoperatively she had extension of her brain damage and was unresponsive. Beta hemolytic streptococcus was cultured out.

This case points up the necessity of establishing blood flow in critical arteries such as the internal carotid. It may be that in the future it would be advisable to try to insert a vein graft even to the divided internal carotid artery, despite the surrounding abscessed tissue.

The sixth patient, a 58-year-old negro male was admitted November 12, 1965, complaining of increasing pain and swelling in his left groin, beginning one week previously. He had been addicted to heroin for 35 years and had recently been injecting drugs into the left femoral vein. Examination revealed a large indurated mass in the left groin measuring 5 to 6 inches in diameter, which appeared to pulsate. A thrill was palpable over the area and a bruit could be heard on auscultation. There was a necrotic ulcer in the center which was leaking blood and pus. The patient, although febrile, refused treatment and signed out against medical advice. However, on November 15, he returned with increased pain and swelling and an enlarged girth of the entire left thigh. No pedal pulse could be palpated on the left. A retrograde aortogram was obtained through the right femoral artery. It revealed a false aneurysmal sac arising from the common femoral artery, with delay and reduction of blood flow into the left leg. The left hypogastric vessel did not opacify. Arteriosclerotic changes were present throughout.

The patient was taken to the operating room and the abscess cavity was opened and drained of considerable clots and necrotic debris. Bright red bleeding ensued from the femoral artery at its bifurcation where the anterior wall was missing for a distance of two inches. It was necessary to ligate the common femoral artery proximally and the superficial and deep femoral arteries distally. The cavity was large and extended proximally toward the pelvis and distally for a distance along Hunter's canal; posteriorly it reached around the femur. The femoral vein had become all but dissolved in the abscess. The wound was left open. The patient was receiving high doses of antibiotics at the time of surgery. Postoperatively, he continued to have a warm left foot with a moderately good capillary flow. This patient resembles the other two with femoral aneurysms. We considered passing a bypass from the iliac to the femoral artery through the obturator foramen. However, drug addiction had destroyed his veins and we would have had to use a prosthetic graft. His infection, however, extended so widely that we considered the chances of avoiding infection to be too slight to warrant this procedure, especially as triple ligature of the femoral vessels in the other cases did not result in gangrene.

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A New Diagnostic Test for Coronary Artery Disease

Using A Coincidence Counting System

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THE DIAGNOSIS of coronary artery disease can usually be made on the basis of clinical history alone. In doubtful cases other procedures are necessary, such as the stress electrocardiogram.[1-3] It is well recognized, however, that an abnormal electrocardiogram may exist in the presence of a normal heart. T-wave inversion or bundle branch block may or may not be an expression of coronary heart disease. These changes, in addition to pathological Q-waves, may also be present in some cardiomyopathies in which the coronary arteries are normal.

Visualization of the coronary arteries by coronary arteriography is at the moment the only method to ascertain more clearly the extent of the disease of the coronary arteries.[4,5] In many individuals the cause of chest pain is obscure, and coronary arteriography is the only means of excluding coronary arteriosclerosis. Even so, coronary arteriography has certain disadvantages: The technique is sometimes difficult and poses discomfort to the patient. The procedure necessitates intra-arterial catheterization and, with the method of Sones,[2] intubation of the coronary arteries. Complications, although rare, are cardiac arrhythmias and myocardial ischemia.[5-7] Technical difficulties sometimes preclude good visualization of the coronary arteries and a trained team is required. In addition, it has been observed that many affected segments of the coronary arteries escape radiologic detection.[8]

For these reasons a procedure which could be performed without discomfort or hazard to the patient and which could be routinely carried out would be desirable. The present report deals with the results obtained in the recognition of coronary artery disease, using a coincidence technique and a positron-emit-

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ting isotope, rubidium^{84} The principle of the test consists of measuring the coronary blood flow using this isotope and comparing the effect of nitroglycerin on coronary blood flow. No attempt is made in this report to describe the technique in detail, the concepts involved in this method, and the mathematical analysis of the data obtained. These have been published in separate communications.[9-11]

Coincidence Counting Method

In the coincidence counting method, pulses are recorded which result from the annihilation of positrons (positive charged electrons, beta-plus) occurring directly between a coincidence pair of detectors. A positron travels a few millimeters inside the body before annihilation with a negative electron, thereby producing two gamma photons directed 180 degrees apart. This is in contrast to the so-called singles technique, which is employed, for example, when rubidium^{86} is used. The singles technique requires heavy lead collimation* around the crystals to limit its field of view; in contrast, in the coincidence method shielding is simplified.

Advantages

Advantages of the coincidence over the singles method are elimination of background noise and a simplified mechanical design. In addition, the activity of the positron-emitting isotopes is in direct proportion to its tissue content and is not a function of the distance of the tissue from the counter, as it is when the singles method is used. The counting rates from structures surrounding the heart do not interfere with the apparatus employed here, and efficiency of the coincidence system is about five times greater than that of a system employing rubidium^{86}. One of the main advantages of the method is that it permits separation of radioactivity of the heart muscle from that of the surrounding tissue. In the apparatus used in these tests two pairs of crystals are used: one pair placed in front and behind the heart respectively; the other symmetrically placed over the right side of the chest (Figure 1). The difference in transmission between the right and the left coincidence counting system is continuously equated electronically and corrected for the presence of the heart and the resulting loss of transmission. This difference in transmission is found by placing a 3-inch stainless steel container with a known dilution of rubidium^{84} successively under the right and left coincidence counters over a predetermined area. The instrument is then electronically aligned to correct for tissue density over both sides of the chest. In addition, a well counter is used, through which arterial blood is drawn at a constant rate. The ratio of efficiency between the coincidence counting pairs and the well counter is less than 1:1,000. Since, in addition, the specific activity in the blood is very small, the disintegrations of rubidium^{84} emanating from the cardiac cavities can be neglected.

The Technique

The myocardial scanning coincidence pair is directed over the left precordium, using an aiming device. The position of the heart

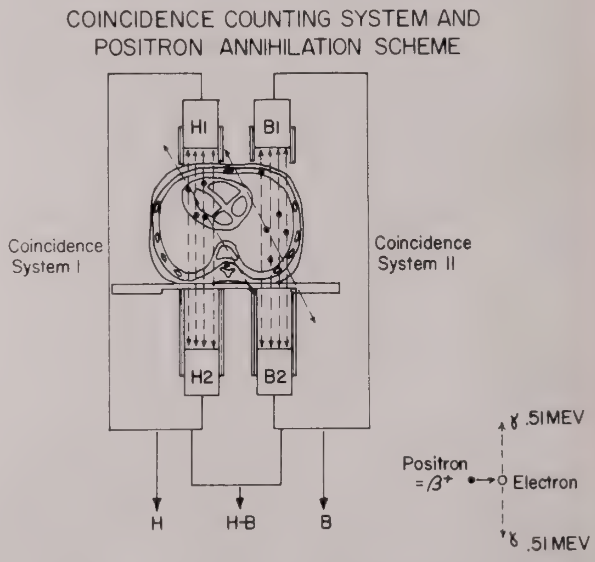

Fig. 1 — Diagrammatic representation of the coincidence counting system and positron annihilation. The two pair of detectors are shown (H_1, H_2 and B_1, B_2). The precordial activity (H) is subtracted electronically from the right chest activity. The difference (H-B) expresses the myocardial radioactivity alone. The right side of the graph shows that when a positron ($\beta+$) collides with a negatively charged electron, two gamma photons with a peak energy of 0.51 MEV are produced. When these gamma photons strike simultaneously the upper and lower detectors of the coincidence pair, a pulse is recorded.

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*See Test Your Word Score Page 97.

is ascertained by roentgenography or fluoroscopy of the chest in the test position. The right side counting pair is placed symmetrically over the right hemithorax above the area of projection of the liver to observe the uptake of rubidium in the chest exclusive of the heart and the liver dome. Uptake of rubidium^{84} by the heart muscle is then expressed as the difference between the left and right sides counting systems (H-B). The apparatus is equipped with a strip chart recorder which prints directly the activity of the left chest (H), the right chest (B), and the difference between these two activities (H-B). The activity of arterial blood as measured in the well counter (A) is also recorded (Figure 1).

After placing the patient under the coincidence counting pairs, 0.4 microcuries of rubidium^{84} per lb. of body weight in 30 ml. of saline are infused intravenously by means of a special motor-driven syringe at a speed of 1 ml. per minute. Simultaneously, arterial blood is drawn from a needle inserted in the brachial or femoral artery. The arterial blood is drawn at a constant speed (7 ml/min.) through a Radicoil inserted into a well counter.

The calculation of the coronary blood flow is based on the Fick principle[12] in which flow is equal to the ratio of the myocardial uptake of rubidium^{84} and the coronary arteriovenous difference of concentration of the isotope. This can be expressed as:

$$1. \qquad \text{Flow} = \frac{dk/dt}{A\text{-}V}$$

where, dk/dt is the myocardial uptake of rubidium^{84} (disintegrations/min.^{2}) and A and V are the radioactivities in the arterial and coronary venous blood (disintegration/ml. x min.) Dividing numerator and denominator in this equation by A, one obtains:

$$2. \qquad \text{Flow} = \frac{\frac{dk/dt}{A}}{\frac{A\text{-}V}{A}}$$

in which, $\frac{dk/dt}{A}$ is the myocardial clearance of rubidium^{84} and $\frac{A\text{-}V}{A}$ is the extraction ratio of rubidium^{84} by the heart. Consequently,

$$3. \qquad \text{Flow} = \frac{\text{Clearance}}{\text{Extraction ratio}}$$

To calculate the coronary blood flow from the myocardial clearance of rubidium^{84}, it is essential to know the influence of coronary flow and heart rate on the extraction ratio. In previous communications[9-11] it was shown in 11 isolated perfused dog hearts and in five patients, in whom the coronary sinus was intubated, that the myocardial extraction ratio declines monotonically with time; changes in flows or heart rate do not alter the slope of the extractions ratio. As the coronary sinus (V) is not intubated during the test, extraction ratio is not known. Based on the above concepts, it is possible to calculate the coronary blood flow by the logarithmic extrapolation of the myocardial clearances to zero time. At this time the radioactivity of the venous blood may be assumed to be zero and that therefore the extraction ratio equals one. This concept has been confirmed experimentally in nine isolated perfused dog hearts with an accuracy between the calculated and observed flows of 93%.[10]

Consequently at time zero:

$$4. \qquad F = \frac{\frac{dk/dt}{A}}{\frac{A\text{-}O}{A}} \quad \text{or} \quad F = \frac{dk/dt}{A}$$

Further details for the calculations of the coronary blood flow in absolute units (ml/min.) are reported in other communications.[9-11]

Calculations were performed entirely by objective analysis carried out with a digital computer. Computer calculations included computation of the myocardial uptake of rubidium^{84}, the first derivative of the uptake, the myocardial clearances, and the coronary blood flow, as well as their standard deviations.

Selection of Patients

The studies were carried out on 10 patients with and on 12 without coronary artery disease. Criteria for the presence of coronary artery disease were a combination of the following: coronary arteriography revealed narrowing and beading of the coronary arteries, a history of recent infarct as substantiated by electrocardiographic and enzymatic studies was present, and a previous infarct was suspected on the basis of history and electrocardiographic findings. The patients ranged in age from 22 to 74 years, nine of them females. Two tablets of nitroglycerin (each 1/150 grain) were administered sublingually after a control period of seven minutes, and the coronary blood flow was followed during one or two periods of seven minutes each after administration of the drug.

Results

In 12 individuals without coronary artery disease the administration of nitroglycerin resulted in a rise in coronary blood flow in six during the first period following the administration of the drug; in eight it remained elevated or increased further during the second period (Figure 2, Table 1). The increase averaged 38 per cent ($P < 0.05$) during the first period and 70 per cent ($P < 0.005$) during the second. In contrast, with the exception of one individual (J. K.), the coronary blood flow failed to rise in nine patients with proven coronary artery disease (Figure 2, Table 2). The average decrease was −14 per cent ($P < 0.025$).

These results demonstrate that nitroglycerin increases the coronary blood flow in patients without coronary artery disease but not in those with coronary artery disease.

Comments

The effect of nitroglycerin as described above is in agreement with several publications.[13-15] The action of nitrites in relieving angina pectoris has been known since 1867, when Brunton[16] described the effect of amylnitrite on a patient suffering from angina pectoris. The effects on the cardiovascular system which bring about the relief of pain are, however, still debated. In dogs nitroglycerin increases coronary flow and decreases cardiac work.[17] A similar effect has also been demonstrated in man. Brachfeld and associates found that in normal man nitroglycerin increased coronary blood flow and myocardial oxygen consumption without elevating the oxygen tension in coronary vein blood.[14] There is evidence that nitroglycerin fails to increase coronary flow in patients with coronary artery disease.[13] Hollander and associates found that nitroglycerin did not increase the rate of clearance of radioactive

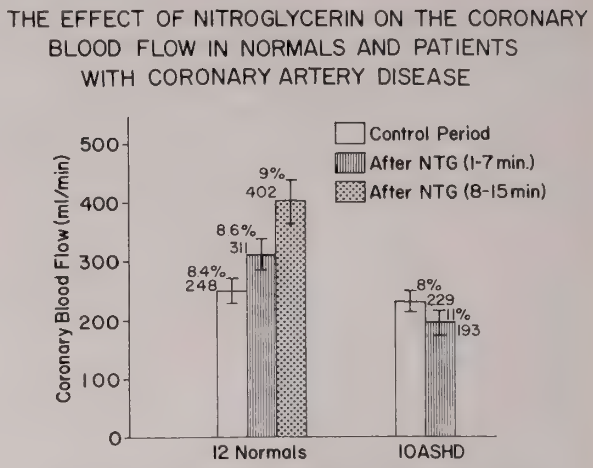

Fig. 2 — The mean coronary blood flow in individuals with and without coronary artery disease before and after sublingual administration of nitroglycerin is shown. It is seen that the coronary blood flow increases in normals but not in patients with arteriosclerotic heart disease.

TABLE I
The Effect of Nitroglycerin in Individuals Without Coronary Artery Disease

Patient Initial	Age	Sex		Percent Change in Flow
M. S.	42	F	I	3 ± 18
			II	−30 ± 19
E. W.	36	F	I	44 ± 38
			II	27 ± 25
E. D.	22	F	I	35 ± 18
			II	26 ± 21
P. E.	35	F	I	−13 ± 18
A. H.	50	M	I	−5 ± 13
			II	26 ± 21
E. D.	29	F	I	44 ± 21
H. P.	32	M	I	−9 ± 11
			II	35 ± 16
P. T.	63	F	I	17 ± 24
			II	126 ± 39
C. P.	74	M	I	86 ± 28
D. H.	22	M	I	−3 ± 15
			II	44 ± 26
E. D.	29	M	I	205 ± 68
			II	295 ± 98
B. H.	53	F	I	46 ± 31
			II	82 ± 39
Average % Change			I	38 ± 25 ($P < 0.05$)
			II	70 ± 34 ($P < 0.005$)
			I	1 to 7 minutes
			II	8 to 15 minutes

sodium iodide from the heart muscle of patients with angina pectoris.[18] Similar results were obtained by others using the nitrous oxide and radioisotope methods.[13-15] It is likely that in normal hearts coronary blood flow increases with nitroglycerin because of a fall in coronary vascular resistance. Although the peripheral coronary vascular resistance may fall in arteriosclerotic patients this effect cannot become manifested because of impediment to flow in the large coronary vessels.[19] Dynamic studies on the action of nitrites have shown that there is a fall in central venous pressure with a decrease in cardiac output and left ventricular work.[13,14,20]

Conclusions

The results reported here confirm the findings of others that nitroglycerin increases coronary blood flow in normal individuals but not in patients with coronary artery disease. This is the basis for the test described here, which differentiates between these two groups. The procedure involves the use of a positron emitter and the coincidence counting system. The advantages of this test are its technical simplicity and objectivity. Catheterization is not necessary and the test lasts no longer than 30 minutes, involving only intravenous infusion of the isotope and an arterial puncture. The data are then processed by a computer which calculates the coronary blood flows in ml/min., together with the standard deviations and the significance of the change in flow prior to and following the sublingual administration of nitroglycerin. The procedure does not permit the measurement of instantaneous changes in the flow because of the high statistical errors when periods of less than five minutes are used.[9-11] It does permit differentiation of patients with and without coronary artery disease with a reasonable degree of accuracy.

TABLE 2
Effect of Nitroglycerin in Patients with Coronary Artery Disease

Patient Initial	Age	Sex	Diagnostic Criteria	Percent Change of Flow	
J. K.	54	F	2	I	−27 ± 12
				II	11 ± 6
C. O.	67	M	2	I	−21 ± 17
J. S.	48	M	2	I	−26 ± 10
S. R.	56	M	2	I	20 ± 23
R. B.	36	M	2.3	I	10 ± 16
N. T.	67	M	2	I	−24 ± 13
K. K.	51	M	2	I	−17 ± 18
C. L.	62	M	3	I	−47 ± 10
J. M.	71	M	2.3	I	−5 ± 18
N. N.	59	F	3	I	−4 ± 16
			Average % Change	I	−14 ± 15 ($P < 0.025$)
				I	1 to 7 minutes
				II	8 to 15 minutes

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The penitentiary of higher education. — Leo Rosten

Pyoderma Gangrenosum

Treated with Sulfone Drugs

PYODERMA GANGRENOSUM is a rare, chronic, ulcerative skin disease which was first described by Brunsting et al.[1] in 1930. The lesions begin as cutaneous abscesses which rapidly break down to form large, peripherally spreading ulcerations with a distinctive purple-red, edematous, and undermined border. The original authors stressed the frequent association of the skin lesions with an underlying chronic debilitating disease, particularly chronic ulcerative colitis.

Later reports confirmed pyoderma gangrenosum as a clinical entity and also noted its association, not only with ulcerative colitis, but with arthritis, foci of infection, hypogammaglobulinemia, and a dermatitis herpetiformis-like vesicular eruption as well.[2-4] In addition, many cases of pyoderma gangrenosum have now been recorded in which no underlying disease state was found.

The disease has a chronic course and during active stages the patient's skin seems to be hypersensitve to both local trauma and to the ingestion of iodides. New lesions may develop at the site of minor or casual skin trauma, while the ingestion of iodides may cause marked aggravation and generalization of lesions.

Oral and parenteral corticosteroids as well as sulfonamides, sulfones, and gammaglobulin have been used effectively in treatment of the disease.[2-5] Control of any underlying condition, such as ulcerative colitis, is of utmost importance since there may be a correlation between the activity of the colitis and the skin lesions.

Case Reports

The purpose of this paper is to report on the treatment and course of two patients with pyoderma gangrenosum, particularly with respect to the use of sulfone drugs in the management of the disease.

Case #1

A 60-year-old white female patient was first seen on December 27, 1962. She was sent to us for follow-up treatment of pyoderma gangrenosum after having been hospitalized at the Mayo Clinic from September through December of 1962.

Past History

The original lesion had appeared as a "pimple" on the abdomen in August 1958. This lesion ulcerated spontaneously and slowly spread to form a large linear ulceration on the left lower quadrant of the abdomen (Figure 1). Subsequently, similar but smaller ulcerations appeared on the right thigh, right shin, and left calf.

The patient had been followed at Henry Ford Hospital from August 1959, through August 1962, being hospitalized twice during that period. Pyoderma gangrenosum was diagnosed, but extensive investigation failed to reveal any underlying ulcerative colitis or infectious focus. During this period the patient experienced one episode of swelling and tenderness of the proximal interphalangeal joint of

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the left ring finger without other evidence of arthritis. Roentgenograms of the finger showed only soft tissue swellings. A trial of salicylazosulfapyridine (Azulfidine) in November 1960 was discontinued, in spite of good initial response, because of development of a "typical morbilliform drug reaction" after nine days of therapy.

In September 1962, when hospitalized at the Mayo Clinic, the patient had four ulcerations varying in size from 17.5 by 5.5 cm. to 1.5 by 5 cm. located on the left lower quadrant of the abdomen, the left calf, the right thigh and the right shin. Oral methylprednisolone (64 mg. per day) was started in September 1962 with gradual healing of these ulcerations. However, in October and November 1962 the patient experienced two acute psychotic episodes requiring care on a closed psychiatric ward. The dose of methylprednisolone was gradually reduced to 21 mg. per day at the time of discharge from the Mayo Clinic in December 1962, when only the lesion on the right shin was active.

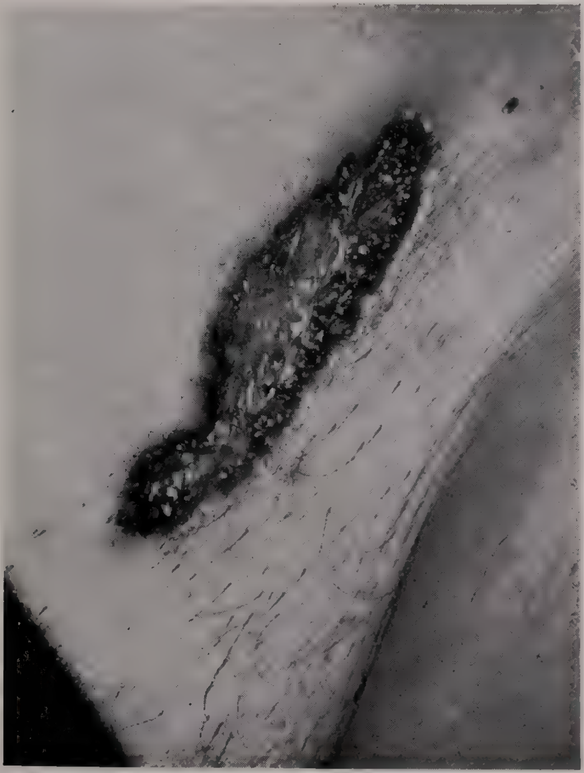

Fig. 1 — (Case 1) Linear ulceration on left lower quadrant of abdomen in 1959.
(Courtesy Dr. T. K. Burnham, Henry Ford Hospital, Detroit, Michigan).

Summary of Laboratory Studies

The value for hemoglobin, the leucocyte count, and the results of routine urinalysis were normal. Sedimentation rate varied from 50 to 65 mm. in one hour (Westergren). Serum electrophoresis showed an increased gammaglobulin (1.37 gm.). Cryoglobulins and macroglobulins were not present. Tests for rheumatoid factor, L.E. cells, and serologic tests for syphilis were negative. Values for blood urea, fasting blood sugar and uric acid were normal. Retention of dye in the sulfobromophthalein test was 0. Skin tests for blastomycin, Coccidiodin and histoplasmin were negative. Skin test for tuberculosis was positive. Repeated cultures of the lesions for bacteria, fungus, and acid-fast organisms revealed no significant pathogens. Microscopic examination of tissue from skin lesions on three occasions and tissue from the nodule on the left ring finger showed only chronic nonspecific granulation tissue. Proctoscopic examination was normal. Roentgenograms of the chest and colon were normal.

Subsequent Course

When first seen by the authors in late December 1962 diaminodiphenylsulfone[*] (Avlosulfon-Ayerst) 100 mg. twice daily was started and steroid dosage slowly tapered. In March 1963 all lesions were completely healed. Steroids and sulfone were then discontinued. The disease remained inactive until May 1964, when the patient developed a new ulceration

1.5 x 2 cm. on the mid-extensor aspect of the right arm. Diaminodiphenylsulfone 50 mgm. twice daily was started along with fluocinolone acetonide (Synalar) cream 0.01% topically with occlusive plastic film. The lesion healed slowly, and in September 1964 sulfones and topical fluocinolone cream were discontinued. Because of hemolytic anemia which may develop in patients on sulfone drugs supplemental iron salts were given along with the sulfone drug; however, no significant anemia developed. The patient has not required systemic steroids since April 1963, and there has been no recurrence of psychotic episodes, as of February 1965.

Case #2

A 59-year-old demolition engineer was first seen on April 10, 1964, because of chronic and recurrent nodular skin lesions over the fingers, knuckles, elbows, knees, soles, and buttocks.

Past History

The original lesion had been noted on the right buttock in 1957. This nodule underwent spontaneous ulceration and healing over an 18-month period. Similar lesions, some of which did not ulcerate, then began to appear over the extensor surfaces. The patient stated that at least one or two lesions had been present continually with intermittent flares for over seven years.

The patient also had diabetes mellitus of three years' duration. The disease was not well controlled because of his erratic use of oral hypoglycemic agents and also because his work as a wrecker kept him continually "on the road," making adherence to a diabetic diet difficult. He stated that he had had a sulfa-drug reaction in 1943. There was no history of asthma, hayfever, urticaria, ulcerative colitis or arthritis.

Physical Examination

Examination of the skin revealed numerous flesh-colored to slightly bluish nodules, varying in size from 0.5 to 3 cm. and situated on extensor surfaces of the fingers, knuckles, elbows, knees, and on the soles and buttocks. The lesions present on the soles and fingers were more bluish and hemorrhagic in appearance (Figure 2) and were painful at times, whereas all other lesions were asymptomatic. The remainder of the physical examination was normal.

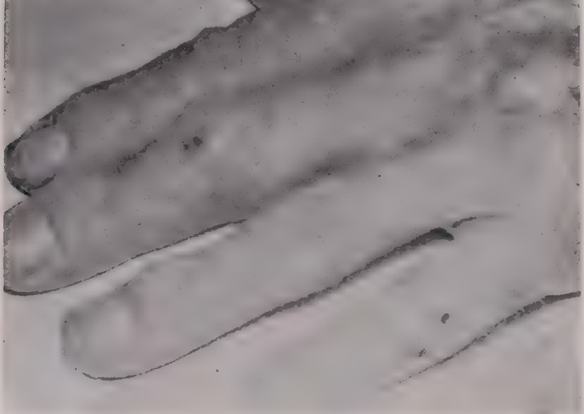

Fig. 2 — (Case 2) Nodules present on the fingers appearing somewhat bluish and hemorrhagic.

Course

The individual lesions appeared to start as areas of deep dermal induration which soon became more superficial and fluctuant and spontaneously exuded a viscid serosanguineous fluid. After draining the lesions healed rapidly with little scarring and without forming the typical chronic ulcerations usually associated with pyoderma gangrenosum. At times some of the indurated areas appeared to resolve spontaneously without becoming fluctuant and without draining.

On June 2, 1964, the patient was started on oral saturated solution of potassium iodide because of the suspicion of sporotrichosis. After taking only 10 drops of potassium iodide solution he experienced a dramatic and profound flare, with marked increase in size and considerable pain in all existing lesions, and with development of new lesions. He was hospitalized at Detroit Memorial Hospital on June 6, 1964.

Laboratory Studies

The value for hemoglobin was 14.8 gm. The leucocyte count was 7900 with 11% eosinophilia. The sedimentation rate varied from 40 to 74 mm. in one hour (Westergren). Routine urinalysis revealed a 4-plus reaction for sugar. The fasting blood sugar was 236 mg. per 100 ml. Other values were urea N 22 mg. per 100 ml., uric acid 5.4 mg. per 100 ml., protein-bound iodine 4.5 mcg. per 100 ml., serum bromide 0 mg. per 100 ml. Serologic tests for syphilis and tests for rheumatoid factor and cephalin cholesterol flocculation were negative. Serum protein electrophoresis showed: albumin 3.8 gm.; alpha-1 globulin 0.4 gm.; alpha-2 globulin 0.7 gm.; beta globulin 1.9 gm.; gammaglobulin 0.6 gm.; and total serum proteins 7.3 gm. per 100 ml. Repeated cultures from nodules for bacteria, fungus, and acid-fast organisms were negative. Smears of material aspirated from the nodules showed no organisms. Roentgenograms of the elbow, chest, colon and upper G.I. tract were normal.

Microscopic examination of skin from an early lesion on the right elbow in April 1964 showed only moderate nonspecific perivascular infiltrate. A second biopsy from a more active lesion on the left elbow in June 1964 showed moderate acanthosis of the epidermis and a diffuse granulomatous infiltrate in the corium consisting of histiocytes, lymphocytes, neutrophils and eosinophils, with some foreign body type giant cells. There were areas of necrosis with accumulation of polymorphonuclear leucocytes forming small abscesses. The findings were those of a chronic nonspecific granuloma (Figure 3). PAS and acid-fast stains were negative.

Subsequent Course

During hospitalization the diabetes was rapidly controlled with diet and insulin. The cutaneous lesions gradually decreased in size and became asymptomatic, and the patient was discharged from the hospital. The differential diagnosis considered at that time was iododerma, atypical pyoderma gangrenosum, and atypical acid-fast infection. The patient was placed on a halogen-free diabetic diet and on an oral hypoglycemic agent. In addition, sodium chloride 4 gm. per day was started in an attempt to remove remaining iodides from the body. However, the patient continued to develop new lesions in spite of elimination of iodides. On June 21, 1964, diaminodiphenylsulfone (Avlosulfon) 100 mg. twice daily and supplemental iron salts were started. Improvement in sulfone therapy was rapid and dramatic. Within two weeks all lesions had become quiescent except for a few scattered ones on the soles. Even these, however, were changed in that they appeared more superficial and vesicular. These vesicular lesions were not biopsied. After three weeks of sulfone therapy the skin was completely clear of lesions for the first time in seven years. This dramatic response to sulfone therapy was in conformity with the diagnosis of pyoderma gangrenosum.

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*Diaminodiphenylsulfone (DDS, Dapsone) is available as Avlosulfon (Ayerst) in 100 mg. tablets.

When last seen in our office on August 7, 1964, the patient had remained free of skin lesions and was on diaminodiphenylsulfone 50 mg. twice daily and supplemental iron salts. A mild anemia (hemoglobin 11.7 gm.) was present.

The patient returned to work in Ohio and subsequently developed an acute penumonia. He was hospitalized and died there on August 17, 1964.

Post-mortem Findings

A post-mortem examination was performed at Miami Valley Hospital, Dayton, Ohio. The gross and microscopic findings were reviewed by the authors (microscopic sections courtesy of Dr. Eric Wenyon, Dayton, Ohio). The cause of death was an acute necrotizing, purulent lobar pneumonia. No organisms were seen in routine sections of the lung nor in those stained for acid-fast organisms and fungus. Skin lesions were not present at the time of death, and therefore no skin specimens were taken. Other significant microscopic findings were: moderate coronary atherosclerosis, centrolobular necrosis of the liver secondary to chronic passive congestion, localized chronic pyelonephritis with marked arteriolar nephrosclerosis.

The cause of death, lobar pneumonia, was felt to be unrelated to the patient's prior skin disease.

Comment

It is now generally accepted that pyoderma gangrenosum is not primarily bacterial or infectious in origin. A hypersensitivity reaction analagous to the Schwartzman phenomenon has been suggested[6] to explain those cases of pyoderma gangrenosum associated with an underlying systemic disease or infectious focus. An autoimmune mechanism has also been postulated, based on some violent antigen-antibody reaction.[5] However, the etiology of the disease remains obscure. The histology of pyoderma gangrenosum is not diagnostic and (as in our two cases) usually shows an ulceration with an associated chronic nonspecific inflammatory infiltrate and an increased number of blood vessels in the corium.[7]

Case 1 presented typical lesions of pyoderma gangrenosum with no underlying disease. The lesions responded well to oral steroid therapy; but this therapy induced two acute psychotic episodes. Good response to oral administration of sulfones permitted rapid tapering of steroids without exacerbation of skin lesions and without recurrence of psychosis. A subsequent flare of the condition responded well to treatment with sulfone drugs and topical steroids alone.

Case 2 presented unusual cutaneous lesions unassociated with other systemic disease. The lesions began as deep abscesses over extensor surfaces which drained and healed without forming spreading ulcerations. The course of the disease was marked by two very dramatic occurrences which we feel confirmed the diagnosis of an unusual variety of pyoderma gangrenosum: (1) A profound flare of all lesions after ingestion of a minimal dose of saturated solution of potassium iodide. (2) An excellent and rapid response to sulfone therapy.

The finding that this patient's skin lesions appeared superficial and vesicular at times led us to believe that this patient might represent a cutaneous phase of the pyoderma gangrenosum syndrome that lies somewhere between the dermatitis herpetiformis-like erup-

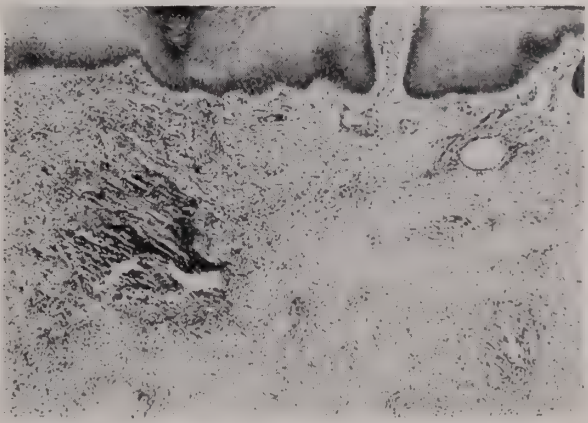

Fig. 3 — (Case 2) Section from active nodule on left elbow showing a diffuse granulomatous infiltrate in the corium. There are areas of necrosis with accumulation of polymorphonuclear leucocytes forming small abscesses. (Hematoxylin and eosin; X60)

tion which has been reported and the more typical undermining ulcerative lesions.

The sulfone drugs have been used effectively in the treatment of leprosy, dermatitis herpetiformis, subcorneal pustulosis and pyoderma gangrenosum.

The sulfones and the sulfonamide drugs have a similar chemical structure but differ in the manner in which sulfur is linked to atoms other than oxygen. In the sulfone drugs these linkages are with two carbon atoms, while in the sulfonamides they are with one carbon and one nitrogen atom. Although the sulfonamides and sulfones are chemically related they do not seem to cross-react with each other.[8] This finding was confirmed in both our patients, since both had a history of sulfonamide allergy but tolerated sulfone drugs well.

Most sulfones are metabolized in vivo to the parent compound, diaminodiphenylsulfone,[9] which is apparently less toxic than other sulfones. We have, therefore, used only diaminodiphenylsulfone (Avlosulfon-Ayerst) in therapy.

Side effects of the sulfone drugs may include hemolytic anemia, cyanosis, methemoglobinemia, and symptoms of anoxia. Nausĕa, vomiting, anorexia, headache, paresthesia, nervousness, and drug eruption may sometimes occur. These toxic effects are readily reversible on withdrawal of the drug.

Since hemolytic anemia of varying but usually mild degree occurs in most patients taking sulfones, it is wise to administer supplemental iron salts and to recommend frequent rest periods for patients on long-term therapy.[9] In general the side effects of the sulfones tend to be temporary and rarely of a severe enough degree to contraindicate continued administration of the drugs.

Sulfone drugs are felt to be less toxic than sulfapyridine in the long-term treatment of diseases such as pyoderma gangrenosum and dermatitis herpetiformis.

Summary

In the treatment of pyoderma gangrenosum it is suggested that sulfone drugs, particularly diaminodiphenylsulfone (Avlosulfon), are effective in the long-term care of this disease.

The sulfone drugs do not produce allergic cross reactions with the sulfonamides and appear to be well tolerated in patients sensitive to sulfonamides.

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The Penalty of Overweight

The inadequacy of pulmonary ventilation in the obese results in decrease in arterial oxygen saturation and an increase in carbon dioxide retention. This derangement can cause somnolence, muscular twitching, cyanosis, secondary polycythemia, and hypertrophian failure of the right ventricle.

Cyril M. MacBryde, M.D., Signs & Symptoms, Lippincott Co.

Massive Intracerebral Hemorrhage

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WILLIAM F. MAHONEY, M.D.*
JAMES W. LANDERS, M.D.*
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CEREBRAL VASCULAR diseases are a major health problem in the United States, ranking as the third leading cause of death in adults.[1] In this country, in 1962, approximately 200,000 people died of these disorders,[1] and it has been estimated[2] that ten times the number who die each year are living victims of cerebral vascular diseases. Increases in the aging population add to the group most susceptible to these conditions.

One of the most common, yet least understood, manifestations of these diseases is massive cerebral hemorrhage. This study presents a brief analysis of the clinical features, morbid anatomy, and theories of pathogenesis of spontaneous massive cerebral hemorrhage, based on patients examined at autopsy in a large emergency hospital.

Materials and Methods

From June 1952 through June 1961, at Detroit General Hospital, 5,799 autopsies were performed on patients over the age of ten. The brain was examined in all but 316 patients, in none of whom was there a question of cerebral hemorrhage.

In all instances, the brain was fixed in 10% formalin at the time of autopsy and sectioned following fixation. Routine and selected paraffin-embedded sections, stained with hematoxylin and eosin, were examined in every case.

The following items, when recorded, were tabulated from each clinical record:

1. Age, sex and race
2. History of hypertension
3. Time from hospital admission to death
4. Characteristics of cerebrospinal fluid
    a. opening pressure
    b. presence of blood
    c. xanthochromia

The autopsy protocols were examined for evidence of hypertensive cardiovascular disease, as reflected by left ventricular myocardial hypertrophy.

For the purposes of this study, massive intracerebral hemorrhage refers to spontaneous hemorrhage within the brain substance greater than 2.5 cm. in maximum diameter; hemorrhages secondary to trauma, blood dyscrasias, ruptured berry aneurysms** or vascular malformations are specifically excluded.

Results

There were 358 patients who died with

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*Departments of Pathology, Wayne State University, School of Medicine, Detroit General Hospital.

**See Test Your Word Score Page 97.

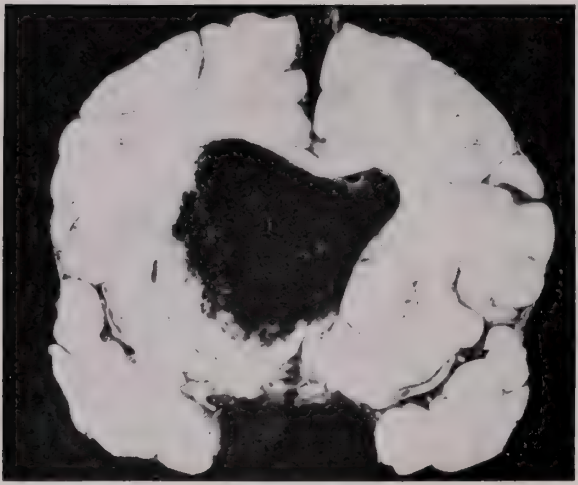

Figure 1

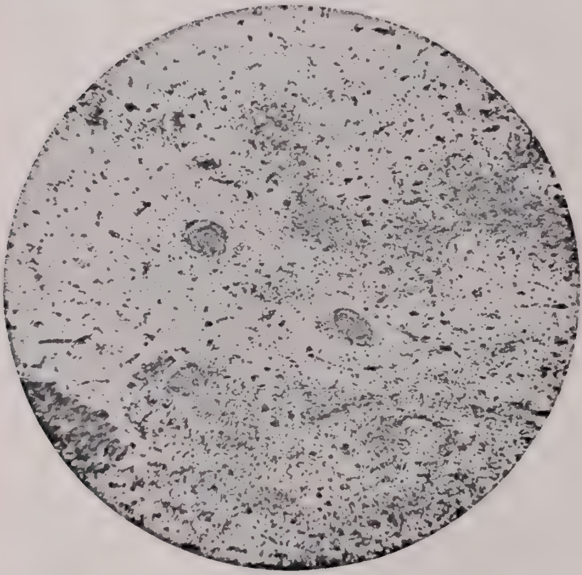

Figure 2

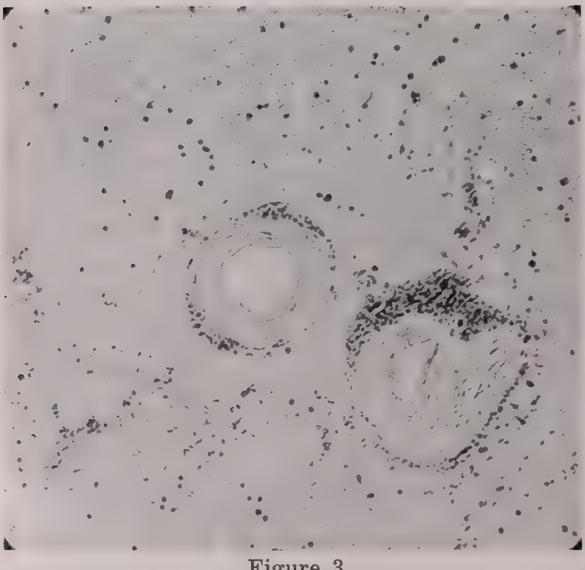

Figure 3

massive cerebral hemorrhage in this series, an over-all incidence of 6.2%. Analysis by age, sex and race is presented in Table 1. The incidence in females was 7.6% and in males, 5.3%; Negroes had an incidence of 8.5%, and whites, 4.4%. When sex and race were combined, the frequencies in descending order were: negro females, 9.4%; negro males, 7.7%; white females, 5.6% and white males, 3.8%.

A history of hypertension and/or anatomic evidence of hypertensive cardiovascular disease was present in all but two of the 358 patients.

Hypertensive Type

Three morphologically different types of hemorrhage occurred in these patients. The "hypertensive type" was found in 75.1%. In these, the brain about the hemorrhage was edematous and contained numerous petechiae (Figure 1). Microscopically, the arterioles at the margin of the hemorrhage showed sclerosis and hyalinization; many were necrotic and permeated or surrounded by red blood cells (Figure 2). About this zone sclerotic arterioles were surrounded by lakes of serum (Figure 3); and arteriolar sclerosis was widespread in the remainder of the brain.

Hemorrhage into Preceding Infarct

Hemorrhage into a preceding infarct accounted for 17.3%. In these, brain swelling about the hemorrhage was less marked, and satellite petechiae were few or absent (Figure 4). Microscopically, arteriolar necrosis was absent, arteriolar sclerosis less severe, and a pre-existing infarct of varying age could sometimes be identified in the margin of the hemorrhage (Figure 5).

Unclassified

Of the cases, 7.2% were labeled "unclassified." In these, although the gross appearance simulated the "hypertensive type," microscopic examination revealed a necrotizing arteriolitis without significant sclerosis or hyalinization (Figure 6).

Location of Hemorrhage

In 58% of the patients, the location of the hemorrhage was in the striate area (bilateral in eight patients); in 20.4%, elsewhere in the cerebral hemisphere (generally the white matter of one or more cerebral lobes); in 12.3%, in the pons; and in 9.2%, in the cerebellum. Rupture into the adjoining ventricle or subarachnoid space, usually the former, occurred in 92%.

Survival Time

The average age at death for the entire series was 56 years. When analyzed by race and sex, however, a significantly lower mean age at death is apparent for Negroes, and especially for negro females (Table 2).

Pons or Cerebellum

Although survival time was shortened when the hemorrhage was located in the pons or cerebellum, the duration of life seemed to correlate better with type of hemorrhage than with location (Table 3).

In Hypertensive Type

Thus, in patients with the hypertensive type of hemorrhage, 65% died within the first 24 hours; 91% were dead by the end of four days; and only two patients survived longer than 10 days.

In Preceding Infarct

By contrast, in patients with hemorrhage into a preceding infarct, 27% died the first day; 58% died in the first four days; and 24% survived beyond 10 days. Survival time for patients in the unclassified group was similar to that for patients with a hypertensive type of hemorrhage.

Elevation of the opening cerebrospinal fluid pressure (over 200 mm. of cerebrospinal fluid) was present in 82.4% of the 245 patients for whom this observation was recorded. The appearance of the cerebrospinal fluid was noted in 260 patients, and in 90% it was bloody and/or xanthochromic.

Discussion

Obviously, the over-all incidence (6.2%) of massive intracerebral hemorrhage is

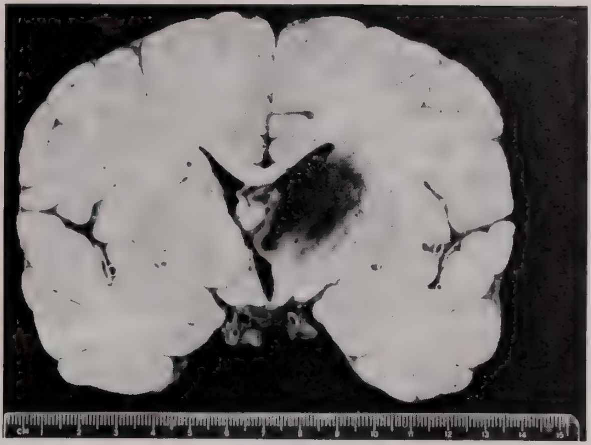

Figure 4

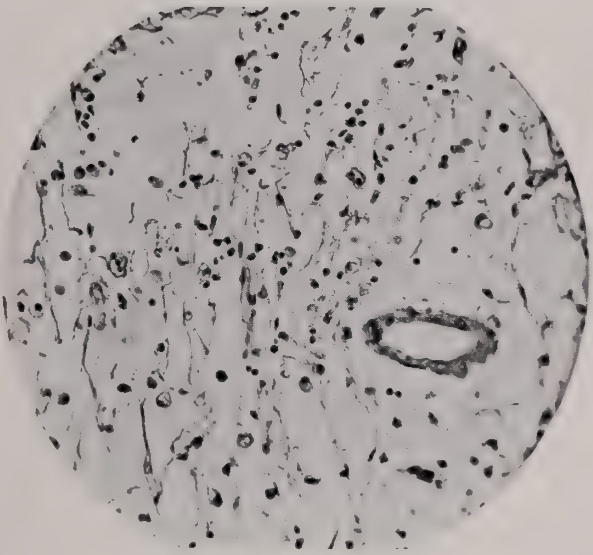

Figure 5

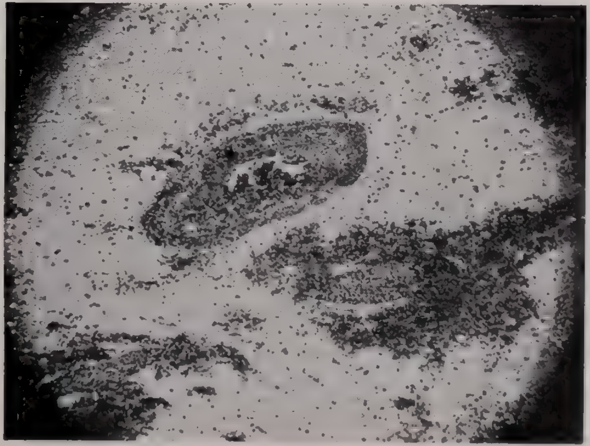

Figure 6

higher than is generally recognized as a cause of death, because of the concentration of such patients in an emergency hospital. Within the group of patients dying from this cause, however, there is no reason to suppose that the figures for sex and race incidence, which have been corrected for the numbers of each sex and race in the total series, are significantly distorted. It is, therefore, we believe, a valid observation that the occurrence of these lesions is more frequent in Negroes than in whites, and within each race a commoner occurrence in females than in males. It is also of interest that the age of onset is significantly lower in Negroes, and especially in negro females.

The morphologic appearance of the hypertensive type of hemorrhage suggests to us that it has its origin in simultaneous and successive rupture of numerous arterioles which, previously sclerotic as part of long-standing hypertensive disease, undergo necrosis for reasons unknown. The hemorrhage into a preceding infarct, on the other hand, probably results from rupture, under the stimulus of increased intravascular pressure, of vessels which are poorly supported externally because of infarction of the surrounding brain tissue. In addition to the differences in morphology and proposed pathogenesis, these two types of hemorrhage exhibit significant differences in length of survival following onset.

This autopsy study necessarily deals only

TABLE 1

	Negro Families		Negro Males		White Females		White Males	
Age	Total Pts.	Cerebr. Hemorr.	Total Pts.	Cerebr. Hemorr.	Total Pts.	Cerebr. Hemorr.	Total Pts.	Cerebr. Hemorr.
11-20	29	1	25	0	9	1	7	0
21-30	77	4	47	1	33	0	28	3
31-40	203	19	160	10	90	1	90	2
41-50	262	38	275	30	97	3	265	9
51-60	244	34	322	34	175	17	454	25
61-70	220	14	293	20	260	20	680	23
71-80	108	2	186	7	227	13	526	18
Over 80	50	0	55	3	134	2	153	3
Unknown	1	0	5	0	1	0	8	1
Totals	1194	112	1368	105	1026	57	2211	84

TABLE 2
Mean Age at Death According to Sex, Race and Type of Hemorrhage

	Hypertensive Type	Preceding Infarct	Unclassified	All Types
Negro Females	49.7	55.8	38.7	49.4
Negro Males	55.4	55.5	47.5	55.0
White Females	62.5	65.8	49.0	63.0
White Males	61.7	66.3	49.2	61.2

TABLE 3
Duration of Survival Following Massive Cerebral Hemorrhage
According to Type of Hemorrhage

Time	Hypertensive Type	Preceding Infarct	Unclassified
0-6 hrs	66	6	4
7-12 hrs.	43	4	3
13-18 hrs	33	4	2
18-24 hrs.	31	3	6
2 days	45	6	7
3 days	13	8	1
4 days	13	5	0
4-10 days	22	11	1
More than 10 days	2	15	2

with patients dying with these disorders, and precise clinical distinction between the two main types of hemorrhage is probably not possible; nevertheless, we believe, on the basis of the evidence available, that prolonged survival following massive cerebral hemorrhage is largely confined to those patients suffering hemorrhage into a previous infarct.

Summary

Massive intracerebral hemorrhage occurred in 358 (6.2%) of 5,799 consecutive autopsies in a large emergency hospital. The lesion was significantly more common, and occurred at a younger age in Negroes, and especially negro females. Hypertensive cardiovascular disease was verified in 99.5% of these patients. The locations, routes of rupture, length of survival and certain characteristics of the cerebrospinal fluid have been discussed.

Based on morphology, three types of cerebral hemorrhage — the hypertensive type, the hemorrhage into a preceding infarct, and an unclassified type — have been described, and their pathogenesis discussed.

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WHAT'S YOUR DIAGNOSIS?

A 22-year-old white married female was admitted to the hospital on 24 February, 1965, complaining of vaginal bleeding and abdominal cramping of one week's duration. Her last menstrual period had begun on 11 January. She had completed two normal pregnancies three and six years previously. Examination revealed a small amount of bleeding from a bluish cervix. The uterus was enlarged to the size of a seven-weeks pregnancy and the urinary pregnancy test was positive. Hgb. was 10.4 gm%. The bleeding subsided and the patient was discharged a few days later with a diagnosis of threatened abortion. She resented her pregnant state and repeatedly requested medication to interrupt the pregnancy, but none was given.

She was readmitted to the hospital two weeks later, again complaining of abdominal cramping and vaginal bleeding, also of a sensation of pressure in the rectum. Her hemoglobin was 9.7 gm% and the pregnancy test was again positive. Pelvic examination revealed a mass in the cul-de-sac extending up into the abdomen and palpable in the suprapubic area. The uterus was firm and somewhat larger than a two months' gestation. A consultant agreed that there was a mass in the cul-de-sac and felt that this was cystic. He suggested that consideration be given to the diagnosis of adnexal neoplasm. Vaginal spotting continued and one week later the mass in the cul-de-sac was found to be laterally larger and now extended up almost to the level of the navel. On the following day laparotomy was performed.

What's your diagnosis? Turn to page 44.

Reputation is what men and women think of us; character is what God and the angels know of us. — Thomas Paine

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A man is getting older when he is going to feel just as well as he ever did in a day or two. — Banking

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Some folks don't go through life — they're merely shoved through it.
— Henry Vance

Thyroid Carcinoma

THE PROTEAN manifestations and often unpredictable natural history of carcinoma of the thyroid are well recognized. Many features of this disease are unique in the field of neoplasia. The cancer may appear in childhood, grow slowly, and be present for many years without causing symptoms. Metastases may be widespread without occasioning overt disability. These metastases, after total thyroidectomy, are sometimes spontaneously stimulated to produce sufficient thyroxine to maintain the patient in a euthyroid or, rarely, hyperthyroid state. Under these circumstances, the tumor may demonstrate a marked avidity for I^{131} and therefore be susceptible to destruction when sufficient dosage of irradiation is delivered by this means. An appreciable number of these metastases are also responsive to the administration of thyroid hormone, presumably through suppression of the thyroid-stimulating-hormone of the pituitary.

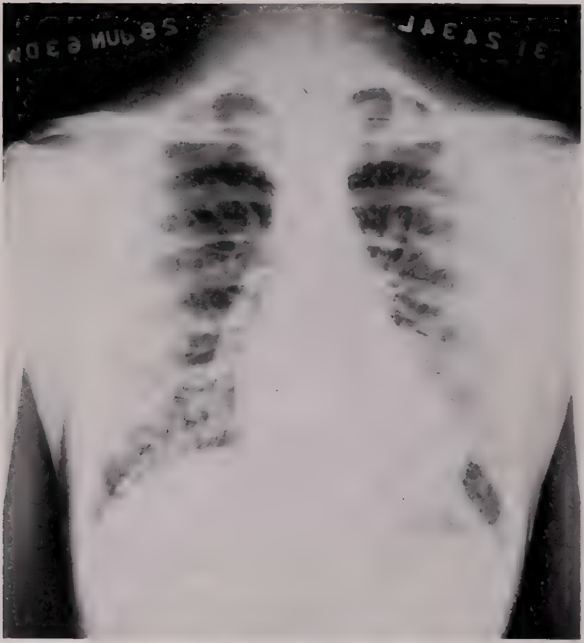
Fig. 1 — Roentgenogram of chest, June 1963. There are multiple irregular nodular densities throughout both lung fields, most numerous at the bases.

In some patients, problems are posed by the benign clinical appearance of the extensive pulmonary infiltration which encourages the diagnosis of sarcoidosis, fungal disease, or healed miliary tuberculosis rather than malignant infiltration. With the diagnosis established in the presence of spread of this degree, modification of the extent of neck dissection may be desirable and the optimal methods of treating residual tumor often rouse controversy. Furthermore, the true efficacy of the pattern of treatment finally selected may be extremely difficult to assess in

Unusual Clinical Features and Problems of Management

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view of the unpredictable natural history of this disease. An unusual number of problems associated with this neoplasm were strikingly illustrated in the following patient.

Case Report

History

A married female, aged 24, was admitted to Detroit Receiving Hospital on October 30, 1959, for treatment of a Bartholin's abscess. On general examination it was noted that she had a nodular thyroid swelling estimated to weigh approximately 100 grams. The right lobe was larger than the left. On direct questioning, she thought that the gland had increased in size over the past year, but she had not experienced any pressure symptoms. A goiter had apparently been present for most of her adult life. There was no exophthalmos and she was clinically euthyroid. The pulse rate was 80, the blood pressure 100/60, and the circumference of the neck 32 inches. There was no history of irradiation to the neck in infancy or childhood and no history of goiter in her family.

Chest X-Ray Opacities

Radiographs of the chest revealed multiple discrete disseminated opacities (Fig. 1). It appeared that these had first been noted in 1950 when she was 15 years old (Figure 2). She had been referred at that time to Herman Kiefer Hospital, a tuberculosis center, following a routine x-ray of the chest. However, repeated examinations and many sputum tests failed to reveal any evidence of tuberculosis then or later. Her growth and development were normal, and serial radiographs of the chest revealed little change with time (Figure 3). In 1960, she was readmitted to Herman Kiefer Hospital for six weeks for further investigation. At this time a scalene node biopsy was performed which was reported as histologically normal.

Thyroid Growth

On June 25, 1963, the patient returned to the thyroid clinic at Detroit Receiving Hospital. She had recently experienced a slight amount of pain in the

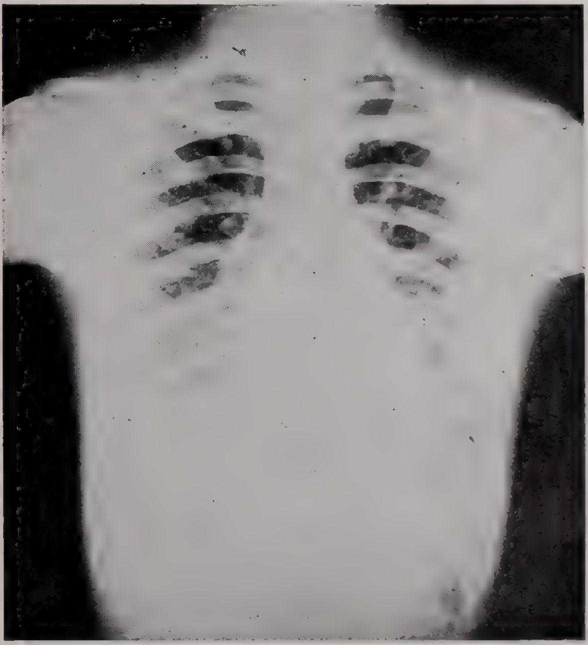

Fig. 2 — Roentgenogram of chest, January 1952. The multiple bilateral opacities in the lung fields show no change from a similar roentgenogram taken in 1950 when patient was aged 15.

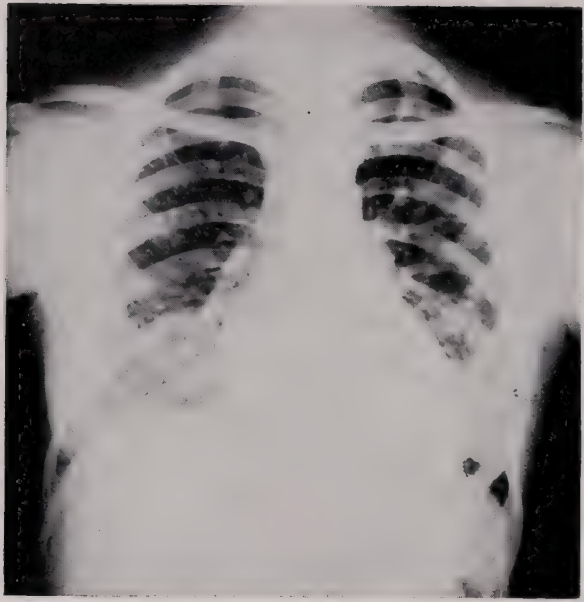

Fig. 3 — Roentgenogram of chest, October 1960. Very slight progression of the pulmonary lesions compared with films of 1952. Patient asymptomatic.

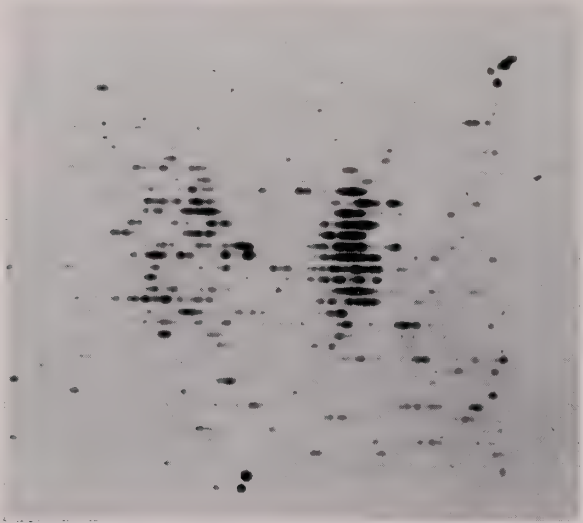

Fig. 4 — Preoperative scintiscan demonstrating irregular uptake in the thyroid gland with nonfunctioning areas, most marked over the isthmus.

region of the right lobe of the thyroid which she thought had become firmer and had grown larger over the preceding six months. She had lost ten pounds in weight earlier in the year but had recently regained this. There was no history of pressure symptoms, changes in voice, hair or skin, or any signs of hyper or hypo-thyroidism. On examination, the right lobe of thyroid was larger than the left and had caused slight deviation of the trachea towards the left side. The thyroid gland was firm and nodular, and a number of discrete lymph nodes were easily palpable laterally in the area of the middle and upper cervical chain, the largest node measuring about 1.8 centimeters. There was no lymphadenopathy palpable on the left side. The rest of the physical examination failed to reveal any abnormalities. The radiographs of the chest taken over the past decade were reviewed, and there appeared to be little change in the most recent film (Figure 1), which showed the same diffuse bilateral opacities that had been present since 1952. Skin tests for tuberculosis, coccidioidomycosis, and histoplasmosis were all negative. A barium swallow on 7/6/63 revealed deviation of the trachea and eosophagus to the left. A roentgenologic survey of the skeleton disclosed no abnormalities. The heart and upper mediastinum were within normal limits. The hemoglobin level was 10.9 grams per 100 ml. Preoperative scintiscan of the thyroid revealed irregular patchy uptake of I^{131} with large hypofunctioning areas (Figure 4).

Operative Procedure and Findings

Operation under general anesthesia was performed 7/10/63. Very early in the operation it became obvious that the strap muscles were firmly adherent to the underlying thyroid gland and that there was abnormal vascularity in the area. In view of this, the strap muscles were incised close to the sternomastoid muscles bilaterally so that these could be removed in continuity with the thyroid; and the largest lymph node, which had been easily palpable clinically, was excised. This measured approximately 2.5 centimeters and was sent for frozen section. Histologically the entire area consisted of thyroid follicles, and no lymphoid tissue could be demonstrated. As the mass was situated in the lateral area of the neck, however, and was separated by at least two inches from the thyroid gland, it seemed that this must be a metastatic lesion, and it was decided to proceed with the operation on this premise. A total thyroidectomy was performed, during the course of which the recurrent laryngeal nerves on both sides were exposed for a considerable distance. It was soon discovered that a chain of hard lymph nodes extended from the lower pole of the thyroid down into the superior mediastinum bilaterally. These nodes were freed from the recurrent laryngeal nerves but were inseparable from the lower parathyroid glands on both sides. They were therefore sacrificed with the specimen. Toward the end of the dissection of the thyroid gland from the trachea it was found that no plane of cleavage existed anteriorly and that it was necessary to excise a portion of the tracheal fascia and cartilage in order to remove the thyroid gland. It was obvious at this point that the deeper portion of the gland was replaced by a large solid tumor which had infiltrated through the posterior surface into the trachea and had actually penetrated through the wall of the trachea over a distance of approximately 3 x 3 millimeters. In addition to this, overt tumor tissue was attached to the trachea over an area of approximately 1.2 centimeters. This tissue was shaved off the trachea. With the thyroid removed, a finger could be inserted into the superior mediastinum. It was noted that a large involved mass of lymph nodes measuring approximately 6 x 5 centimeters was present in the area behind the manubrium. By careful dissection, this mass of metastatic lymph nodes was removed from the superior mediastinum.

The right and left upper parathyroid glands were identified and preserved, but it was noted that their vascular supply was precarious because of their close attachment to the involved lymph nodes and the surrounding inflammatory process.

With proven involvement of the trachea, extensive invasion of lymph nodes in the superior mediastinum, and the preoperative demonstration of presumably metastatic lesions throughout both lung fields, bilateral neck dissection was felt to be unnecessarily aggressive in these specific circumstances. Consequently, only the nodes immediately adjacent to the internal jugular veins were removed. In view of the penetration of the tumor into the trachea and the anticipated need to deliver heavy postoperative radiation in this area, a tracheostomy was established at the conclusion of the procedure.

Pathology

The gross specimen measured approximately 10 x 8 x 3.5 centimeters. The right lobe was larger than the left and the entire anterior surface was nodular (Figure 5). The central area of the gland, particularly over the region of the isthmus, was replaced by solid yellowish-tan colored tumor tissue which had completely replaced the posterior surface in the midline and had transgressed the thyroid capsule (Figure 6). The lymph nodes submitted varied in size from 2 x 2 millimeters to 2 x 2 centimeters and were tan-grey in color. Histologically the tumor showed features of a follicular adenocarcinoma with varying degrees of differentiation ranging from solid masses to well-differentiated follicles filled with colloid (Figure 7). Part of the capsule of the thyroid was infiltrated and involvement of the perichondrium of the trachea was noted in some of the sections (Figure 8). No papillary component was found in the multiple sections that were examined.

Progress

Postoperatively both vocal cords moved normally but the patient developed severe tetany 48 hours after surgery. The serum calcium fell to 5.2 milligrams percent. She was treated with intravenous calcium gluconate and was gradually brought under control with calcium lactate orally, amphogel, limited dairy products to reduce phosphorus absorption, and ultimately between 150,000 and 300,000 units of vitamin D daily. This tetany has remained permanently. In addition, the patient was initially given three

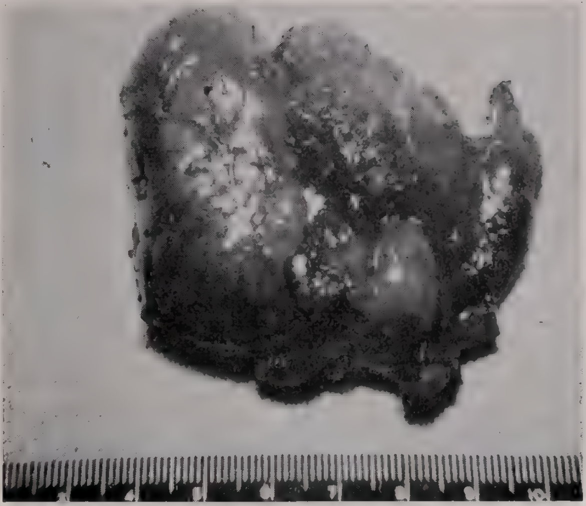

Fig. 5 — Operative specimen following total thyroidectomy. Anterior surface. Attached strap muscles have been removed to show irregularity of the surface.

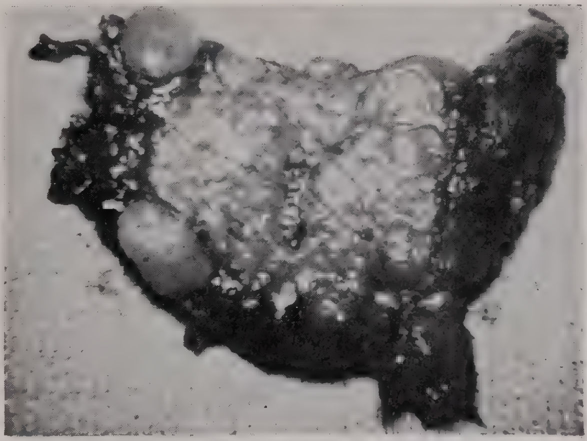

Fig. 6 — Operative specimen viewed from posterior aspect. The central area of the thyroid has been replaced by solid infiltrating tumor.

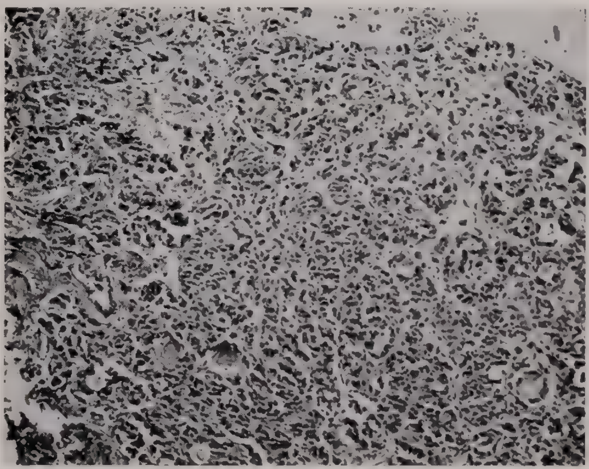

Fig. 7 — Follicular adenocarcinoma showing a mixture of follicles of varying size and solid areas of moderately well-differentiated malignant cells. (X90)

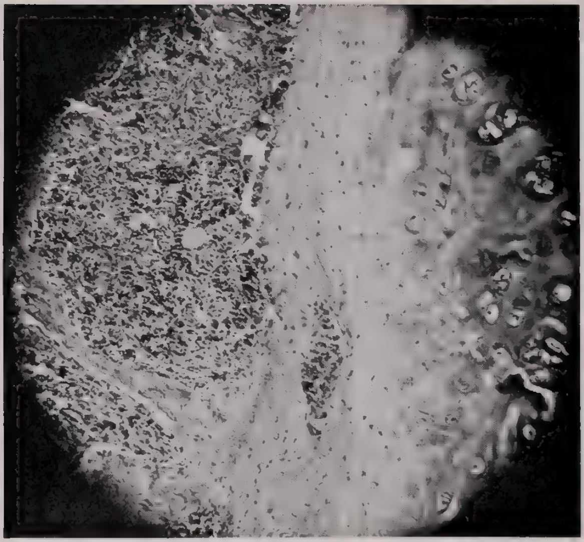

Fig. 8 — Involvement of perichondrium of the trachea by the tumor. Tracheal cartilage is on the right. (X90)

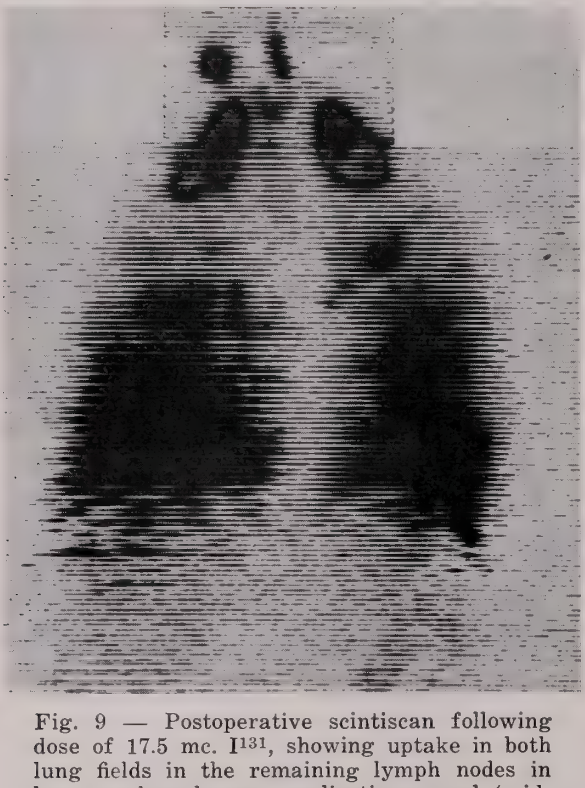

Fig. 9 — Postoperative scintiscan following dose of 17.5 mc. I^{131}, showing uptake in both lung fields in the remaining lymph nodes in lower neck and upper mediastinum, and (midline superiorly) over the small residual infiltration of the trachea. The density below this is due to the presence of a temporary tracheostomy tube.

grains of thyroid extract daily as hormonal replacement but soon developed symptoms suggestive of toxicity on this dosage, finally stabilizing on 1½ grains of thyroid extract daily.

Radioactive Iodine Studies

After she had recovered from the immediate effects of the operation, she received 17.5 millicuries of I^{131} purportedly for purposes of carrying out a complete body scan on 7/31/63. This scan (Figure 9) revealed metastatic nodes on both sides of the neck, a small area immediately above the tracheostomy tube and extensive bilateral pulmonary infiltration. After considerable discussion by members of the thyroid clinic of the optimal treatment but without final unanimity of opinion, it was decided to administer a therapeutic dose of I^{131} for the purpose of treating the area of tracheal involvement above the tracheostomy tube and to follow this with heavy irradiation of the same area. One hundred millicuries of I^{131} was given on 8/7/63 and was followed by 5,000 R of external irradiation to the area of the tracheal involvement between 8/22/63 and 10/25/63.

Follow-up

The patient continued to be followed through 1964. It was noted that no symptoms or signs of hypothyroidism developed when she was taken off thyroid extract for six weeks prior to a scintiscan for the purpose of delineating the residual metastases. The protein-bound iodine and butanol-extractable iodine at this point were 4.5 and 3.8 micrograms percent respectively. During this period of thyroid withdrawal she developed an accentuation of her tetany, and the vitamin D dosage was temporarily increased to 300,000 units daily with an increase in intake of calcium lactate orally. Under this regimen serum calcium has fluctuated between 8.2 and 10.4 milligrams with the phosphorus remaining at approximately 4.5 milligrams percent. Between 1/10/64 and 1/12/64, ten units of thyroid stimulating hormone was given daily, following which a scintiscan was carried out once again. No change in the metastases was observed and a bone survey was negative. On 2/5/64, 150 millicuries of I^{131} was given. Scintiscans on 2/28/64 and 5/29/64 performed after appropriate preliminary cessation of thyroid hormone revealed no significant change in the extent or distribution of the metastases except for disappearance of uptake over the tracheal area. On 12/17/64, pulmonary function tests were performed by Dr. B. Lewis to serve as a baseline for future observation. These revealed a moderate decrease of vital capacity and diffusing capacity without obstruction to air flow. The findings were as follows (anticipated normal in parentheses): Vital capacity 2,516 cc. (3,260); One-second vital capacity 1,914 cc. (2,930); Maximum expiratory velocity 237 L./Min. (400 L.); Maximum mid-expiratory flow rate 115.8 L./Min. (216 L.); Maximum breathing capacity 74.5 L./Min. (86 L.) 13.0 ml/mmHgxmin. (17.5).

When last seen in February 1965, the patient was taking two grains of thyroid extract, 10 grams of calcium lactate, and 200,000 units of vitamin D daily. She was in excellent condition and completely asymptomatic except that she is now three months pregnant with her sixth child. Radiographs of the chest showed regression of the pulmonary opacities (Figure 10).

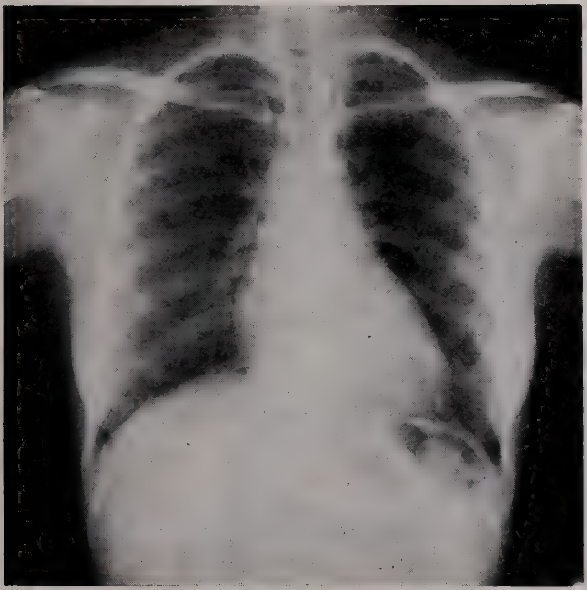

Fig. 10 — Roentgenogram of chest, February 1965. Marked regression in size and extent of pulmonary metastases.

Discussion

It has become well recognized over the past decade that carcinoma of the thyroid is an unusual but not rare malignancy of childhood and adolescence,[1] associated in a significant number of cases with prior irradiation of the neck or thymus. Some of these young patients have presented with widespread discrete pulmonary metastases which give rise to the so-called "snow flake" effect radiologically and yet have had few if any subjective symptoms. Some of these patients, like ours, are mistakenly diagnosed and treated as having tuberculosis or sarcoidosis on the basis of these radiological findings. Furthermore, this pathological picture is compatible with comfortable and perhaps asymptomatic survival for many years, especially if the tumor is responsive to hormonal influences and therefore susceptible to treatment with thyroid hormone as first described by Dunhill in 1937.[2] We have been able to document in this patient the fact that her pulmonary involvement was well established by the time she was 15 years old and that it had apparently progressed little in the 15 years that had since elapsed, despite the absence of any treatment. This makes the objective assessment of the results of treatment very difficult and stresses the need for long-term follow-up periods in thyroid malignancies.

Therapy

Therapy has posed some unusual problems and has involved many different modalities. The principle of surgical removal of as much of the primary lesion as possible was followed. It was recognized that the tracheal involvement was the area of greatest immediate hazard and that, although the obvious area of infiltration was excised, some residual involvement probably remained. This was later confirmed on I^{131} tracer studies. Administration of preoperative I^{131} and the use of a probe at the operating table to detect residual radioactivity as advocated by Dobyns may have been useful. The possibility of a partial tracheal resection with prosthetic replacement or major resection with the establishment of permanent tracheostomy was entertained but rejected in view of the known extensive pulmonary involvement. Results with the former have been unsatisfactory, and the latter procedure was considered to be unjustifiably mutilating. Instead, with the overt tumor excised, considerable reliance was placed on subsequent radiotherapy, both external and by I^{131}, in the hope that this would sterilize the small amount of residual neoplasm in this region. In view of her pregnancy, no recent scintiscan of this area is available. It should be noted, however, that absence of uptake of I^{131} in this region which has had heavy irradiation does not necessarily ensure absence of tumor. It is possible that neoplastic cells altered by irradiation remain viable but have merely lost the capacity to concentrate iodine.

In spite of the widespread involvement of both lungs, the patient has little impairment of her pulmonary function tests. Both pulmonary and lymph node metastases were demonstrated to have a marked affinity for I^{131}. It was therefore vital in determining therapy that considerable thought be given to the possibility that massive doses of I^{131} delivered to diffuse, receptive metastases of this magnitude might produce iatrogenic disability and subsequent death through the mechanism of radiation fibrosis, as has been documented by Rall et al.[3] Consequently, after administering 250 millicuries I^{131} without any immediate change, it was decided to avoid further doses unless the lesions showed significant progression. One year after the last dose, however, radiographs of the chest demonstrate regression of the metastatic lesions. Nevertheless, this benefit cannot be unequivocally ascribed to I^{131} therapy as she has been on thyroid hormone continuously since thyroidectomy and the regression may be due to hormonal suppression.

Pregnancy

Finally, the present pregnancy has also posed special problems. While there has been speculation in the past about the possible exacerbation of thyroid malignancy by pregnancy, there is no convincing evidence to support this concept. We are concerned, however, about the possibility of injury to the fetus from the large quantities of vitamin D on which the patient depends for control of her tetany and which may conceivably pass the placental barrier. If the fetus has a sustained iatrogenic hypercalcemia resulting from a high blood vitamin-D level, the possibility of the syndrome of supra-aortic valvular stenosis, mental retardation and facial changes occurring must be considered.[4] It was decided that there is not sufficient evidence at the present time to warrant termination of the pregnancy; but the effect on the fetus will be very carefully observed.

Summary

A female patient who had widespread bilateral pulmonary metastases from adenocarcinoma of the thyroid at the age of 15 remained asymptomatic and untreated until the age of 28 when she presented with an enlarging goiter. Despite total thyroidectomy and removal of many involved lymph nodes, she has sufficient residual functional tissue to maintain a state of euthyroidism. Although she still has widespread metastatic involvement both in the neck and in the lungs, she remains in excellent health.

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Derivatively Speaking

Alopecia: from Greek alopekia, baldness of foxes

The Carcinoid Syndrome

Circulatory and Cardiac Manifestations

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MALIGNANT ARGENTAFFINOMAS of the bowel or lung when associated with liver metastases may give rise to the carcinoid syndrome.[1] About one half of these patients exhibit certain cardiovascular changes attributed to the pharmacological properties of serotonin or 5 hydroxy-tryptamine.[2,3] Recent work suggests that the protean clinical manifestations may be due to other vasoactive agents in addition to serotonin. Histamine and other active analogues of serotonin have been detected in significant amounts in the circulating blood of these patients.[4,5] Robertson and his co-workers[6] were able to produce flushing in patients with the carcinoid syndrome by the intravenous administration of epinephrine, and on the basis of their experiments, questioned that serotonin is the agent mediating the flush. In an attempt to elucidate the effects of serotonin on the cardiovascular system and to search for other circulatory substances that may be contributory, we have studied the circulatory hemodynamics and measured the blood histamine and catecholamines** as well as serotonin levels in a recent patient with the carcinoid syndrome.

Case Report

A 60-year-old white male was admitted to the Dearborn Veterans Administration Hospital for the first time on February 2, 1964. His symptoms had begun insidiously approximately two years prior to admission. He complained primarily of persistent diarrhea and episodes of facial flushing and sweating, associated with weakness, abdominal cramps and diarrhea, and a sensation of persistent fullness in the epigastrium which seemed to be getting worse over the two-year period. He had a poor appetite, felt that he was becoming progressively weaker, and had noted a weight loss from 220 to 182 pounds. He denied any paroxysms of breathlessness associated with these episodes. However, he had experienced some exertional dyspnea which had been getting worse in the few months prior to his admission, when it was associated with some swelling of the ankles. He had been admitted to another hospital on January 25, 1964, where an exploratory laparotomy was performed and an 8 x 10 cm. mass in the left lobe of the liver was biopsied. There were also two metastatic nodules in the right lobe. He was then transferred to this hospital.

Physical Findings

On the initial physical examination his blood pressure was 198/100. There was noted a reddish malar flush, and the patient appeared to be sweating excessively. The neck veins were not distended. The anteroposterior diameter of the chest was increased disproportionately for the patient's age. The maximal intensity of the heart beat was felt 2 cm. to the left of the midclavicular line. There was a Grade III/VI systolic murmur along the left sternal border between the second and fourth intercostal spaces. The rhythm was regular; the rate, 80. The abdomen was visibly distended in the epigastrium and left upper quadrant. There was a firm mass about 8 x 10 cm., which was thought to be in the left lobe of the liver, whose edge could be palpated 7 cm. below the xiphoid and 12 cm. below the right costal margin. The edge of the spleen was palpable just below the left costal margin. There was a 2+ pitting pretibial edema and telangiectases noted over the face and the upper part of the trunk.

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**See Test Your Word Score Page 97.

Laboratory Findings

The hemoglobin was 16 grams; hematocrit, 45%; alkaline phosphatase, 7 Bodansky units; total serum protein, 6.8 gm.% with a globulin of 1.4 gm.% and an albumin of 4.7 gm.%. The total serum bilirubin was 1.8 mg.% with a direct bilirubin of 0.9 mg.%. The transaminase was 22 units. The urine was positive for 5 hydroxy-indole-acetic acid with the nitroso-naphthol reagent.[7] An electrocardiogram showed left ventricular hypertrophy. A chest x-ray revealed cardiomegaly, pulmonary congestion, and changes compatible with pulmonary emphysema. An upper gastrointestinal series, a barium enema, and an intravenous pyelogram were all normal.

The patient's hospital course was characterized by refractory congestive heart failure and progressive hepatosplenomegaly. He was noted to have episodes of sweating and facial flushing and persistent diarrhea. His blood pressure ranged from 115/90 to 198/100, but hypertension could not be correlated with the above episodes, nor could pressure on the tumor mass elicit such an episode.

Biopsy

The liver biopsy showed the parenchyma to be compressed and displaced by poorly circumscribed nests and sheets of small cells with the alveolar pattern of carcinoid type of adenocarcinoma (Figure 1). Dilated and congested anastomotic venous channels surrounded and apparently lined by tumor cells were a striking feature in many areas (Figure 2). A few small glands, some of which contained inspissated amorphous eosinophilic material in the lumens, were present in other less well differentiated areas of the tumor.

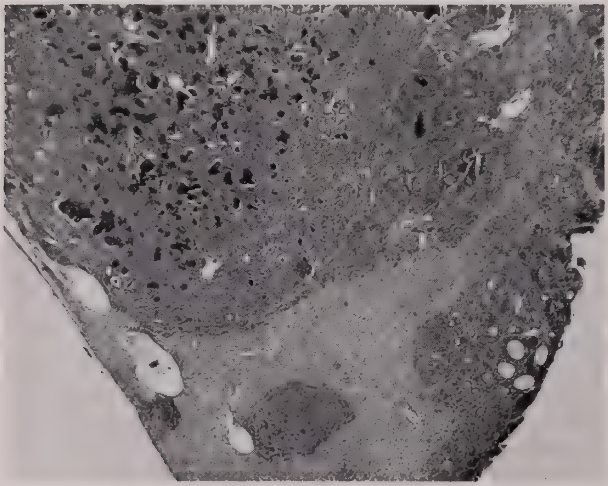

Fig. 1 — Wedge biopsy of liver which is infiltrated by metastatic carcinoid tumor. H&E x 6.5.

Arteriogram

Right heart cardiac catheterization and a pulmonary arteriogram were performed, at which time hepatic vein, peripheral artery, and vein blood samples were drawn for determination of serotonin, catecholamines, and histamine. He did not experience any flushing during catheterization. The results of the cardiac catheterization are presented in Table 1, and the blood determinations in Table 2. Simultaneous pulmonary artery and right ventricular pressure tracings are shown in Figure 3 and a pulmonary arteriogram in Figure 4.

The patient was treated with digitalis, cyproheptadine hydrochloride (Periactin), and hepatic artery infusion of 5 fluoro uracil. His progress was complicated by occurrence of an acute myocardial infarction from which he has recovered. He remains alive, but his course is compatible with progressive tumor growth.

Methods

Blood gases were measured by the method of Van Slyke, and cardiac output was determined by the Fick method.

The protocol for the measurement of serotonin was as follows: 0.5 ml. of blood was pipetted into a 40 ml. glass-stoppered centrifuge tube, followed by 0.5 ml. of distilled water, 1 ml. of ascorbic acid — edathamil reagent (300 mg.% ascorbic acid in 1% edathamil disodium salt), 1 gm. of sodium chloride, 3 ml. of 0.1 M borate buffer pH 10 and 7 ml. of butanol. The contents were mixed by gentle swirling for 10 minutes and then centrifuged at 2000 r.p.m. for 15 minutes. Five ml. of the butanol layer was then introduced into another glass-stoppered centrifuge

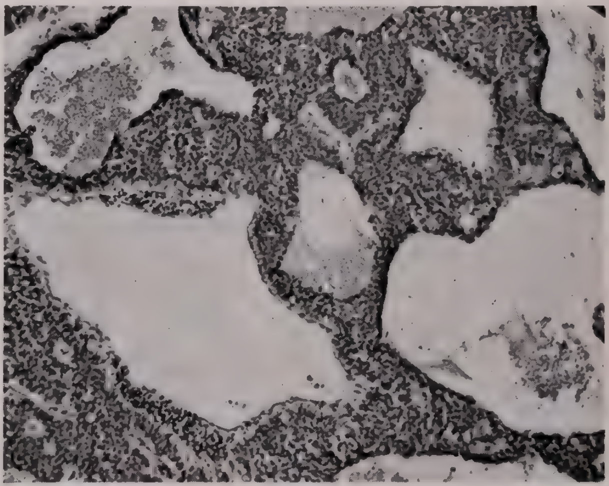

Fig. 2 — Portion of metastatic carcinoid which contains venous "lakes." H&E x 65.

tube containing 7 ml. of heptane and 5 ml. of 0.1 N Hcl. The contents were mixed thoroughly and centrifuged. Three ml. of the hydrochloric-acid extract was pipetted into a quartz cuvette (Turner No. 110-802) and 1 ml. of concentrated Hcl was then added to it and mixed. The fluorescence was then measured in a Turner fluorometer equipped with Far Ultra Violet Lamp (Turner No. 110-851). The primary filter used was a combination of Corning No.'s 7-54 and 0-53 (297 mu) and the secondary filter was a Corning No. 2A-12 (350 mu). The concentration of serotonin in the sample was determined by comparing its fluorescence with a serotonin standard.

Histamine was determined following the method described by Shore.[8] Total catecholamines were determined by the method of Price and Price.[9]

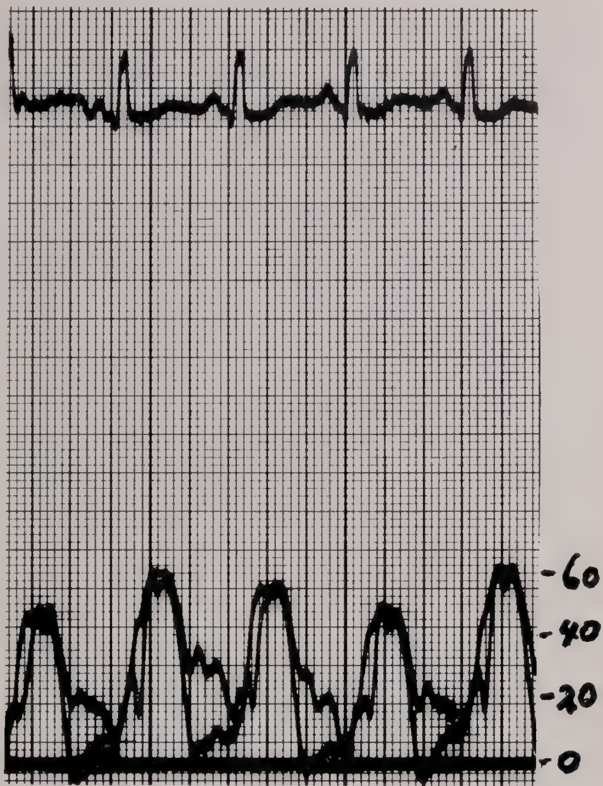

Fig. 3 — Simultaneous pulmonary artery and right ventricular pressures.

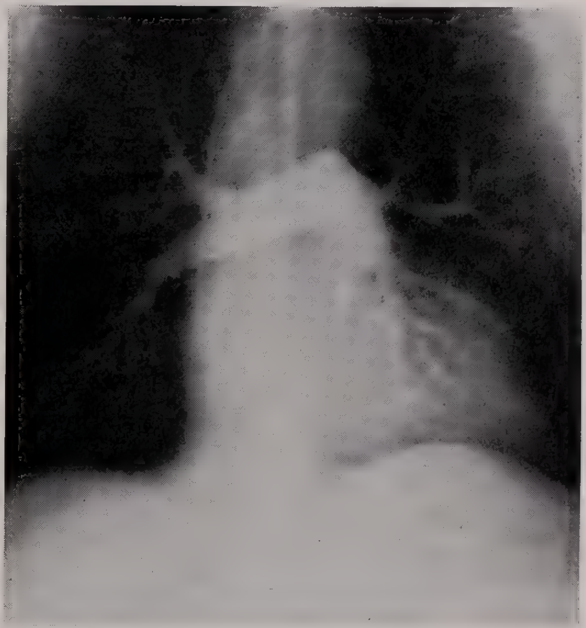

Fig. 4 — Pulmonary arteriogram.

Discussion

McKusick[10] has reserved the term "carcinoid syndrome" for those patients who exhibit cardiovascular changes. The lesions in the heart are chronic endocarditis and valvulitis, which are quite distinct histologically from those produced by rheumatic fever. These changes are observed primarily on the right side of the heart affecting the pulmonary and tricuspid valves, frequently resulting in functional stenosis or regurgitation. The nearly complete preponderance of these lesions on the right side of the heart has been explained by the inactivation of serotonin as it circulates through the lungs. Goble,[11] by sampling blood from the pulmonary and the brachial arteries simultaneously, found that two thirds of the serotonin in the pulmonary artery is removed from the blood during passage through the lungs, presumably by a monoamine oxidase in the lung, which converts 5 hydroxy-tryptamine to 5 hydroxyindoleacetic acid, a pharmacologically inactive degradation product. However, Sjoerdsma[3] has measured serotonin levels in pulmonary artery, antecubital vein, right atrium, and femoral artery, and was able to detect no significant differences. The left side of the heart has been involved, and mitral and aortic lesions have been found in patients with patent foramen ovale with some right to left shunting of blood.[10,12] Recently a case has been reported[13] of carcinoid heart disease with left-sided endocardial and valvular lesions found at post-mortem examination, with a closed foramen ovale and no lung metastases. This patient also had right-sided heart lesions which were much more severe than those found on the left side.

Increased Pulmonary Pressure

The prominent feature of the catheterization data in our patient was the markedly elevated pulmonary artery pressure and increased pulmonary arteriolar resistance. The pulmonary wedge pressure, an indirect measurement of left atrial pressure, was within normal limits, which would indicate that pulmonary arteriolar constriction or obstruction, rather than pulmonary venous constriction, was responsible for the elevated pulmonary artery pressure. The elevated right ventricular pressures and right atrial pressures were a reflection of some degree of right heart failure, probably secondary to the increased pulmonary resistance. This patient clinically was not in left heart failure at the time of the study; however, there were previous clinical indications of associated left heart failure. He had systemic hypertension and associated changes of left ventricular hypertrophy by x-ray and by electrocardiogram. As he subsequently suffered an acute myocardial infarction, it is presumed that he had arteriosclerotic heart disease. Thrombosis is a prominent feature of the carcinoid syndrome; and when it occurs in the lung, it may be partially responsible for the elevated pulmonary artery pressure. Occlusion of small parenchymal arteries of the heart by thrombosis resulting in myocardial infarction without occlusion of the major coronary vessels has been demonstrated.[10] The cardiac index in this patient was low and could be a result of the obstruction of the pulmonary arteriolar bed or a reflection of disease of the left side of the heart. Low cardiac output in the carcinoid syndrome has been reported by Wood[14] and Schweizer.[13] To our knowledge an increased cardiac output has never been reported in the carcinoid syndrome. There was no indication in this patient of valvulitis, either stenosis or regurgitation. Simultaneous pulmonary artery and right ventricular pressure tracings showed no systolic gradient across the pulmonary valve, and there was no evidence of tricuspid stenosis from the right ventricular diastolic and right atrial pressure tracings. Injection of dye into the pulmonary artery revealed no regurgitation through the pulmonary valve.

TABLE 1
Cardiac Catheterization Data

	Rest	Exercise
Pulmonary wedge pressure: mm Hg	(10)	
Pulmonary artery pressure	55/18 (25)	62/22 (53)
Right ventricular pressure	55/0-10	62/5-12
Right atrial pressure	(10)	
Hepatic wedge pressure	(10)	
Hepatic vein pressure	(10)	
Cardiac rate	84	105
Cardiac index: L/min/M^2	2.1	2.3
Pulmonary arteriolar resistance: dynes/sec/cm^{-5}	271	
Total pulmonary resistance	452	

(parentheses denote mean pressures)

TABLE 2
Histamine, Serotonin and Catecholamine Levels
(Micrograms Per Liter of Blood)

Type of Blood	Histamine	Serotonin	Total Catecholamines
Arterial blood	121	360	1.36
Hepatic vein blood	113	350	0.34
Peripheral vein blood	110	321	2.04
Normal values	40-100	90-180	0.1-0.85

Serotonin Level

In our patient the serotonin level was increased in the hepatic vein, in a peripheral arm vein, and in arterial blood. This is in agreement with previous studies by Sjoerdsma,[3] and by Pernow and Waldenstrom.[4] Peart and his group[5] could demonstrate no rise in serotinin in serial blood samples from a catheter in the hepatic vein during a flushing attack induced by intravenous epinephrine. The approximately equal serotonin levels in the hepatic vein, the peripheral arm vein, and the arterial blood indicate a steady release of serotonin from the tumor; and the absence of any significant rise in serotonin in hepatic vein blood during an episode of flushing casts doubt on the etiological role of serotonin in precipitating the flush, and perhaps in other vasomotor phenomena observed in the carcinoid syndrome. The lack of any detectable difference between the venous and arterial concentrations of serotonin indicates that there was probably no significant inactivation of serotonin in the pulmonary vascular tree.

Histamine

We also found elevated and approximately equal histamine concentrations in the hepatic vein, peripheral vein, and arterial blood. It has been postulated by Waldenstrom[15] that serotonin triggers the release of histamine, and it is the histamine which is responsible for some of the manifestations of the carcinoid syndrome, such as flushing and sweating. Whether histamine is secreted by the tumor cells in the liver, or whether histamine release from the liver and other sites is stimulated by serotonin,[16] or whether the increased activity of a decarboxylase enzyme in converting 5 hydroxy-tryptophane to serotonin may also decarboxylate histadine to histamine as well,[15] the result would be the same: increased histamine blood levels, approximately equal in hepatic vein, peripheral vein and arterial blood, as observed in our patient. However, some investigators[17] have found normal histamine levels in blood and urine in the presence of elevated serotonin levels.

Rosenberg and his group[18] have reported the close relationship and interaction between endogenous circulating epinephrine, norepinephrine, and serotonin in producing the vasomotor changes associated with hemorrhagic and endotoxin shock. This relationship has also been demonstrated in anaphylactic shock.[19] It has been repeatedly shown that exogenous epinephrine or norepinephrine can produce a typical flush in the carcinoid syndrome.[5,20] This work raises the interesting question of the possible role of the catecholamines in the carcinoid syndrome. The level of catecholamines in the hepatic vein in our patient was normal; however, there was significant elevation of the catecholamines in the peripheral vein and in arterial blood. This would indicate that the catecholamines were not being liberated by hepatic metastases, but probably by the adrenal medulla. Whether this release is triggered by serotonin is uncertain. However, our patient did have increased catecholamine activity in the peripheral blood, and it is quite possible that interaction or balancing of concentrations of these endogenous circulating vasoactive substances results in blood pressure fluctuations and episodic flushing and sweating.

Summary

This patient with a histologically proven diagnosis of carcinoid tumor of the liver, exhibited some of the typical cardiovascular changes: increased pulmonary artery pressure and pulmonary arteriolar resistance with a normal pulmonary wedge pressure. The serotonin levels in the hepatic vein, in a peripheral arm vein, and in arterial blood were all abnormally high, and approximately equal. We also found abnormally elevated serum histamine levels in hepatic vein, peripheral vein, and arterial blood. The catecholamine levels were elevated in the peripheral vein and in arterial blood but were not increased in the hepatic vein. This would indicate that there are other vasoactive substances present in the circulating blood of the carcinoid syndrome besides serotonin, which may play a role in the manifestations of this disease.

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3-20 May be secured from the author or the reprints.

Fear not that thy life shall come to an end, but rather fear that it shall never have a beginning. — Cardinal Newman

IT'S THE LAW

Association of Doctors Treated as Corporation for Income Tax Purposes

An association of doctors operating a clinic under articles of association similar to those used by corporations should be treated, for federal income tax purposes, as a corporation rather than a partnership, although state law prohibits the formation of corporations for the practice of medicine and most of the association's income came from personal services, a federal trial court ruled.

In June, 1960, two doctors who had operated a clinic as a partnership for a number of years formed an association to operate it. The articles of association, similar in form and substance to those used by corporations, vested management in a Board of Governors.

The association took over the assets and liabilities of the partnership, and all employees of the partnership became employees of the association.

The Board of Governors held regular weekly meetings of a corporate board of directors. All payments for medical services were placed in the association's bank account. Social Security Tax and income tax were withheld from the pay of all employees, including the doctors, and the required reports were filed with the government.

The government took the position that, for federal income tax purposes, the association should be treated as a partnership instead of as a corporation. In determining whether an organization qualifies as an association taxable as a corporation, the corporate characteristics of centralized management, continuity of life, transferability of interests, and limited liability must be considered. The association satisfied the first three criteria, the court said. No association could satisfy the fourth.

The fact that state law forbids the formation of corporations for the practice of medicine was not grounds for denying the association the status of a corporation for tax purposes, the court said.

Foreman v. U. S., 232 F. Supp. 134 (D.C., Fla., April 2, 1964) — Citation Vol. 10, No.4.

ANSWER TO WHAT'S YOUR DIAGNOSIS

(From page 31)

At surgery the pelvis was found to be filled with a large retroperitoneal hematoma containing one liter of blood. The hematoma rose within the right broad ligament, filled the retroperitoneal pelvic area and apparently destroyed the right tube, because this was not identified. The left tube and ovary and the right ovary were normal. In spite of entertaining a strong suspicion of vaginal instrumentation, no evidence of trauma could be found in the region of the cervix or vaginal vault. The uterus was slightly enlarged but otherwise normal. The pathologist reported a large amount of clotted blood, but also described a fallopian tube with chorionic villi and chronic salpingitis. Final diagnosis was ruptured right tubal pregnancy with an extensive pelvic retroperitoneal hematoma involving the right broad ligament.

Finish every day and be done with it. You have done what you could. Some blunders and absurdities no doubt crept in; forget them as soon as you can.

— Emerson

Patch-Grafting of the Gastrointestinal and Urinary Tracts*

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THE FINDING that a defect in the gastrointestinal tract may be patch-grafted with the seromuscular surface of an adjacent loop of bowel allows the surgeon to widen a narrowed area or bridge a defect. Experimentally this approach has been used successfully in closing large defects of the distal esophagus[1] and the duodenum,[2] and in reconstruction of the esophagogastric junction,[3] the urinary bladder[4] and the ureteropelvic junction.[5] Clinically the method has shown promise in the management of spontaneous perforation of the esophagus[6] and of acid peptic stricture of the distal esophagus, and also in achalasia.[7]

Development of the Technique

The concept of patch-grafting arose from the difficulties encountered in managing injuries of the lateral wall of the second portion of the duodenum. After the wound edges were debrided, there was a lack of tissue for adequate closure. A similar problem was encountered when the lateral wall of the duodeum was involved by a right-sided hypernephroma or carcinoma of the hepatic flexure of the colon. It seemed that the application of the serosal surface of an adjacent loop of bowel might bridge the defect and that the resulting shallow ulcer formed by this reconstruction might in time be covered by an ingrowth of adjacent bowel mucosa. Experimental studies, using the duodenum as a model,[4] proved this hypothesis to be correct (Figure 1). In all areas of the bowel where it has been tried, with the important exceptions of the stomach and first portion of the duodenum, healing of these patch-grafts

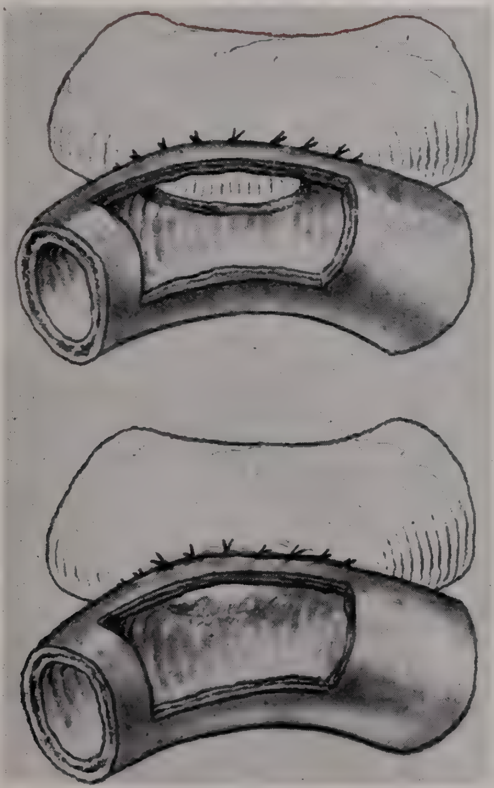

Fig. 1 — Application of patch over duodenal defect showing the ingrowth of duodenal epithelium over the surface of the adjacent loop of bowel.

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**Robert S. Marx Laboratories, Department of Surgery, Wayne State University School of Medicine, Detroit, Michigan, Receiving Hospital and Dearborn VA Hospital.

takes place initially by the formation of granulation tissue on the seromuscular surface of the patch, followed by rapid growth of low cuboidal epithelium in the intestine and by flattened squamous epithelium in the esophagus. After eight weeks the duodenal patch is covered by a well-developed surface layer of duodenal mucosa showing a villous structure quite comparable to that in the adjacent duodenum.

Patch-Grafting of the Distal Esophagus and Esophagogastric Junction

Among the nonmalignant problems involving the distal esophagus, spontaneous perforation and stricture continue to challenge the surgeon. In our experience with the Boerhaave syndrome, patients who are also alcoholics often reach the hospital many hours or days after the perforation has occurred. At the time of exploration, there is mediastinal abscess and empyema; the edges of the perforation are hemorrhagic and necrotic. Our previous experiences in attempting primary closure of this form of advanced perforation has been uniformly unsuccessful. After application of a patch-graft of the stomach fundus drawn through an incision in the diaphragm, we have had primary healing in patients who have experienced perforation between 24 and 48 hours prior to operation. The operation is simply performed through a left lateral thoracotomy and is combined with vagotomy, gastric drainage procedure and gastrostomy (Figure 2).

A similar technique has been used in the treatment of distal esophageal stricture. By making an incision in the long axis of the stricture the problem becomes one of coverage of an anterior wall defect. After dividing the vasa brevia the fundus is mobilized and sutured over the anterolateral walls of the esophagus. In this way the normal caliber of the esophagus is restored and at the same time a flap valve is formed at the esophagogastric junction. The serosal surface of the stomach now facing into the esophageal lumen comes to be lined with squamous epithelium. In Figure 3 the application of the gastric fundus is depicted. Not only does it afford maximal widening of the esophagogastric junction but, by forming a double fold of fundus, a long valve-like entry of the esophagus into the stomach is secured, thus protecting against reflux esophagitis.

The Use of the Patch-Graft as an Experimental Gastric or Duodenal Ulcer Preparation

Hitherto, attempts to create gastric and duodenal ulcers operatively resulted in spontaneous and rapid healing. The use of the

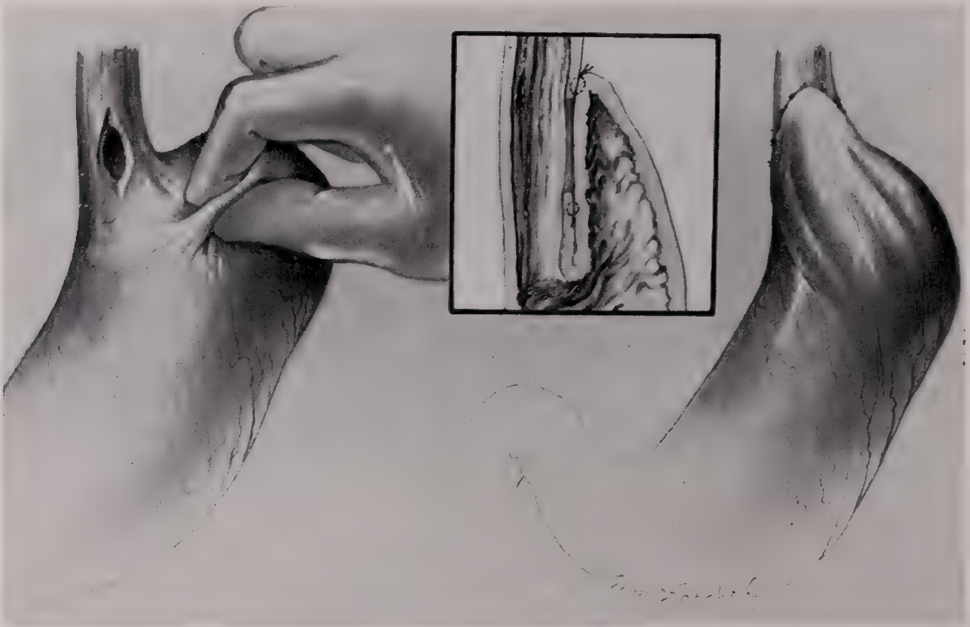

Fig. 2 — Patch-grafting of spontaneous perforation of the esophagus.

patch procedure to attain this objective was suggested by the finding that in the stomach and first portion of the duodenum healing of the patch failed to occur in over 70 per cent of animals; persistent ulceration and ultimately perforation of the patch into the bowel loop often developed. The experimental preparation is illustrated in Figure 4. A standard full-thickness defect, usually 2 cm. in diameter, is created with a cork borer in the dependent portion of the body of the stomach or first portion of the duodenum. Then an adjacent loop of bowel is sutured circumferentially, thereby creating a full-thickness ulcer. Control studies revealed that approximately 60 to 70 per cent of animals with this experimental ulcer have either persistent ulcer or fistula six weeks after operation, and when these animals are stimulated with histamine in beeswax the fistula rate is approximately 100 per cent. When meas-

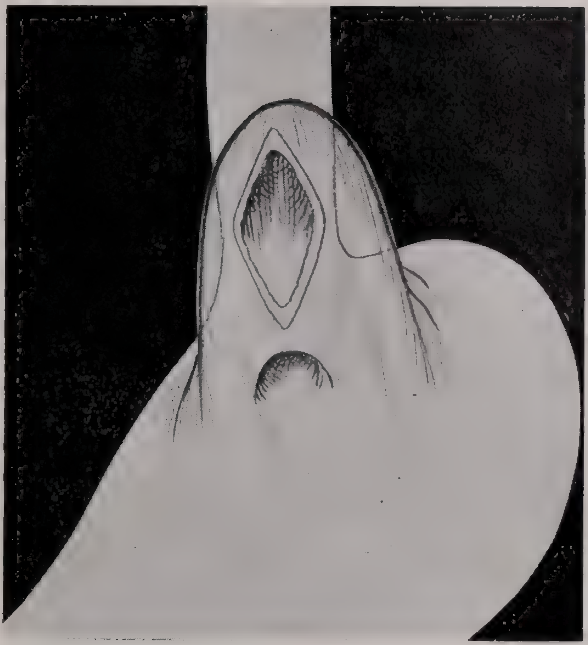

Fig. 3 — Fundic patch reconstruction of esophageal stricture.

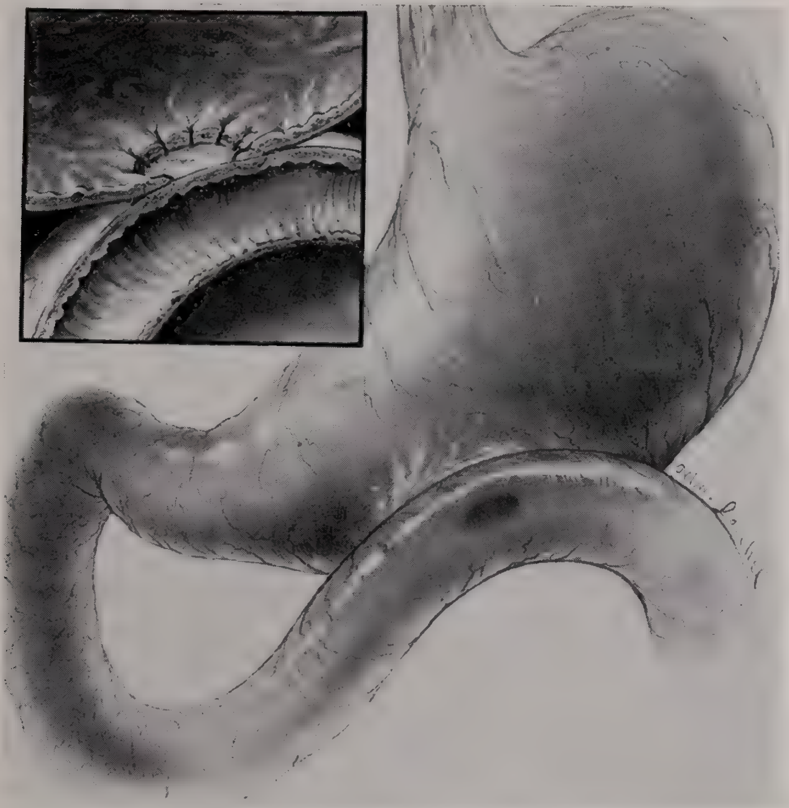

Fig. 4 — Experimental gastric ulcer preparation. A full-thickness defect is created in the stomach and patched with the seromuscular layer of an adjacent loop of bowel. Approximately 70 per cent of these persist as chronic gastric ulcers or form a fistula with the loop. When the preparation is stimulated with histamine, persistent gastric ulcer develops in all. The same preparation can be created in the first portion of the duodenum as an experimental duodenal ulcer.

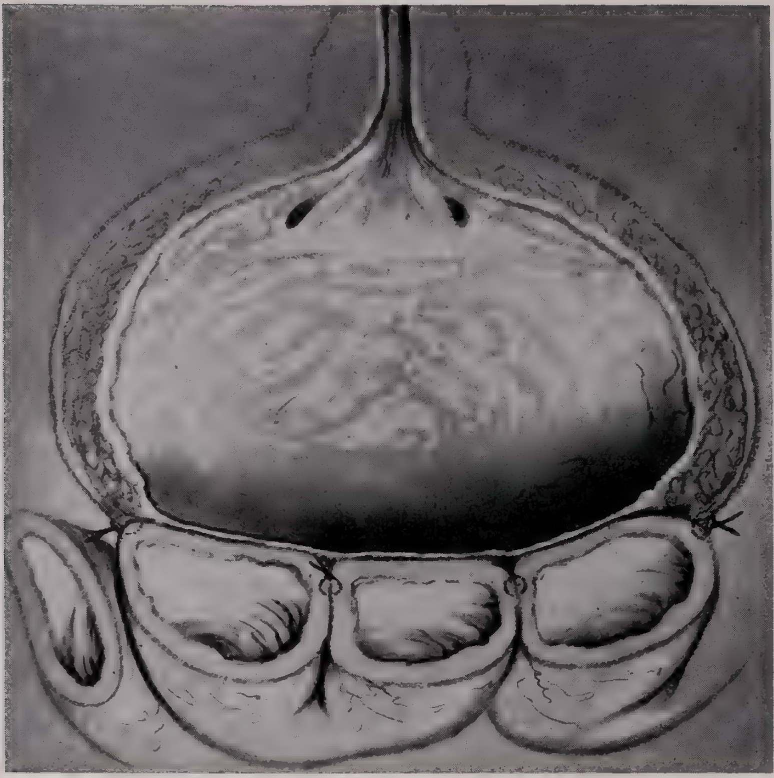

Fig. 5 — Bladder defect sealed by application of several loops of small bowel. Growth of bladder mucosa occurs across the seromuscular layer of the small bowel.

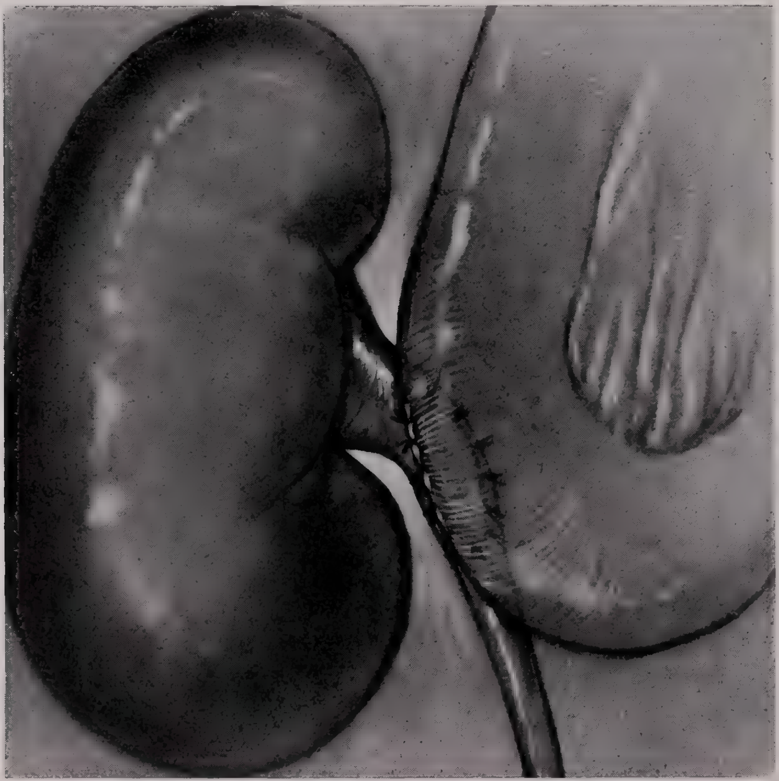

Fig. 6 — Defect in the ureteropelvic junction is patched by the application of an adjacent loop of duodenum.

ures are taken to ablate acid production, healing is rapid and uniform. The preparation appears to be of value in studying any procedure designed to suppress parietal cell activity in the intact stomach. It may be used to study the effect of anticholinergic drugs, of vagotomy, or of gastric freezing or radiation. After vagotomy, for example, approximately 90 per cent of experimental ulcers are healed and relined by gastric or duodenal mucosa within six weeks.

The Use of the Patch-Graft in the Urinary Tract

In the genitourinary tract problems may arise in regard to wide excision of a bladder tumor leaving a small residual urinary pouch, or with strictures occurring at the ureteropelvic junction. To both these problems the use of gastrointestinal patch-grafting may offer a solution worthy of clinical trial (Figures 5 and 6). Considerable enlargement of the dog urinary bladder can be secured by the use of three loops of small intestine plicated together in Noble fashion and applied directly over the defect with running catgut sutures. This enlarges the bladder, and regeneration of transitional epithelium occurs readily across the surface, enlarging the bladder without encroaching on the lumen of the bowel. Whether or not electrolyte and water absorption occurs across the intestinal patch applied to the bladder has yet to be studied.

Finally, the ureteropelvic junction may be enlarged by incision in the long axis followed by application of a conveniently situated loop of bowel as a patch-graft. In the human and in the dog, the second portion of the duodenum suffices well for reconstruction of the right ureteropelvic junction.

Summary

A method of patch-grafting defective or stenotic areas of the gastrointestinal and urinary tracts is described. The defect which is already present or which is created by incision through an area of stenosis is reconstructed by insertion of a patch of adjacent bowel wall. The seromuscular surface of this patch now facing into the lumen comes to be lined by mucous membrane native to the area.

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A hundred times every day I remind myself that my inner and outer life are based on the labors of other men, living and dead, and that I must exert myself in order to give in the same measure as I have received and am still receiving.

— Albert Einstein

Mother Nature is a remarkable woman, but she still can't jump from summer to winter without a fall, or from winter to summer without a spring. — Ray D. Everson

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Vanity is the death of good living. — Balzac

Pulmonary Surgery

Certain patients with pulmonary emphysema develop cystic spaces which are anatomically located immediately beneath the visceral pleura.[6] On occasion the entire hemithorax seems to be filled by giant nonfunctional air cysts, while the remaining lung is compressed and becomes atelectatic. (Figure 1). We would like to re-emphasize that patients with this type of pulmonary pathology can be said to have "surgical emphysema"; for one can expect functional improvement with a properly planned and executed surgical procedure.[4,5,7,8]

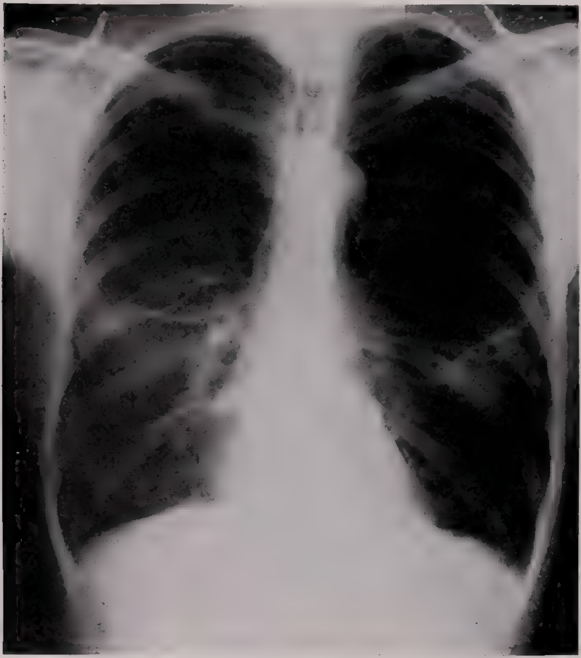

Fig. 1 — Bilateral space-occupying air cysts resulting in vanishing lung fields in the upper lobe areas. This location is typical in patients with giant bullous emphysema.

The Nature of the Patient

During the last eight years, 23 male patients with bullous emphysema have had 27 surgical procedures performed for this condition at the Dearborn Veterans Hospital. Their average age was 41 years, the range being 32-55. One patient had been treated for clinical asthma.

Excessive Smoking

All smoked more than one pack of cigarettes per day. Timed vital capacity and maximum breathing-capacity determinations were obtained before the operative procedure and serially postoperatively when possible.

Pulmonary Distress

The reason for hospital admission is given in Table 1. Only four patients had no pulmonary symptoms. Three were admitted because abnormality of the chest roentgenogram was noted. The patient with pancreatitis had no symptoms referable to his chest but was found to have a fluid-filled pulmonary cyst from which the tubercle bacillus was later recovered. In addition to the eight patients that were admitted with pneumothorax, four others had a previous history of this complication. It is interesting that dur-

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for Emphysema

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ing this eight-year period only four patients have been operated upon for respiratory insufficiency alone.

Tuberculosis Cysts

Five patients had fluid-filled cysts and two were found to have tubercle bacilli as the cause of the fluid. Another patient, treated preoperatively with streptomycin, had the histologic appearance of tuberculosis, but acid-fast bacilli were not cultured from the specimen. A typical case is seen in Figure 4 with multiple fluid levels. A previous chest x-ray taken one year earlier demonstrated the air spaces without the fluid.

There was no operative or late mortality and there were no serious complications in the 23 patients.

Procedures

Cystectomy and Obliteration of the Pleural Space

In 17 operations on 15 patients the surgical procedure was limited to a wedge resection of the blebs or simply unroofing the air sacs and ligating the bronchial communications. The remaining functional lung parenchyma was re-expanded to fill the hemithorax. The pleural space was obliterated by gauze abrasion of the pleura or by partial parietal pleurectomy.

It was found that patients with the poorest pulmonary function derived the most benefit from the surgical procedure. If the vital capacity was less than 75% of the predicted value, improvement was routine. The excep-

TABLE I

Diagnosis	No. of Patients
Pneumothorax	8
Pneumonia	4
Respiratory insufficiency	4
Bullous emphysema no symptoms	3
Possible tuberculosis	3
Pancreatitis	1
	23

The admitting diagnosis in 23 cases with giant bullous emphysema.

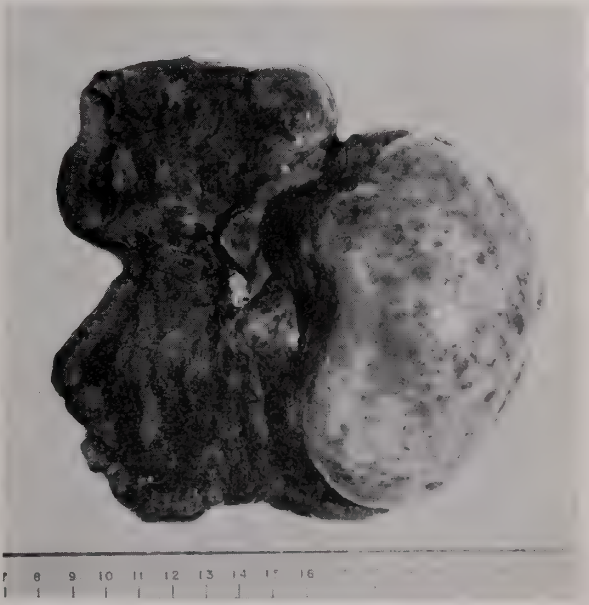

Fig. 2 — The specimen of a right upper lobe lobectomy of Patient #23. The lobe itself is somewhat emphysematous but capable of some function. The cyst remains expanded on the visceral pleura.

tions were the oldest patient, #8, and the patient with asthma, #9. Of the six patients whose pulmonary functions were greater than 75% of the predicted, only one had significant improvement after resection of emphysematous blebs.

There has been to date no recurrence of pneumothorax or x-ray evidence of giant air-cyst recurrence.

Segmentectomy and Lobectomy

It was thought best by the operating surgeon to remove a segment or a lobe in nine patients (10 operations). Figure 2 demonstrates the resected right upper lobe of patient #23. Figure 3 shows the apical and posterior segments of the right upper lobe in patient #16. It can be seen that a portion of the lobe and segments deflate while the cysts remain inflated. The deflated lung had functional potential, and it was noted that whenever segmental resection or lobectomy was done, potentially functional lung tissue was removed as well as cystic lung.

Table 3 demonstrates that pulmonary

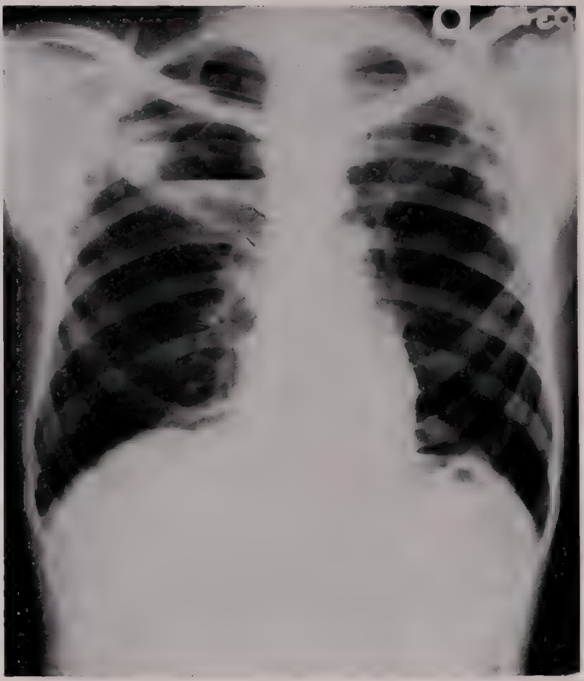

Fig. 4 — Air-fluid levels in patient #13 who was admitted with pancreatitis. A previous x-ray had demonstrated bullous emphysema in the right upper lobe area. Smear and culture of the fluid removed at surgery was positive for tubercle bacilli.

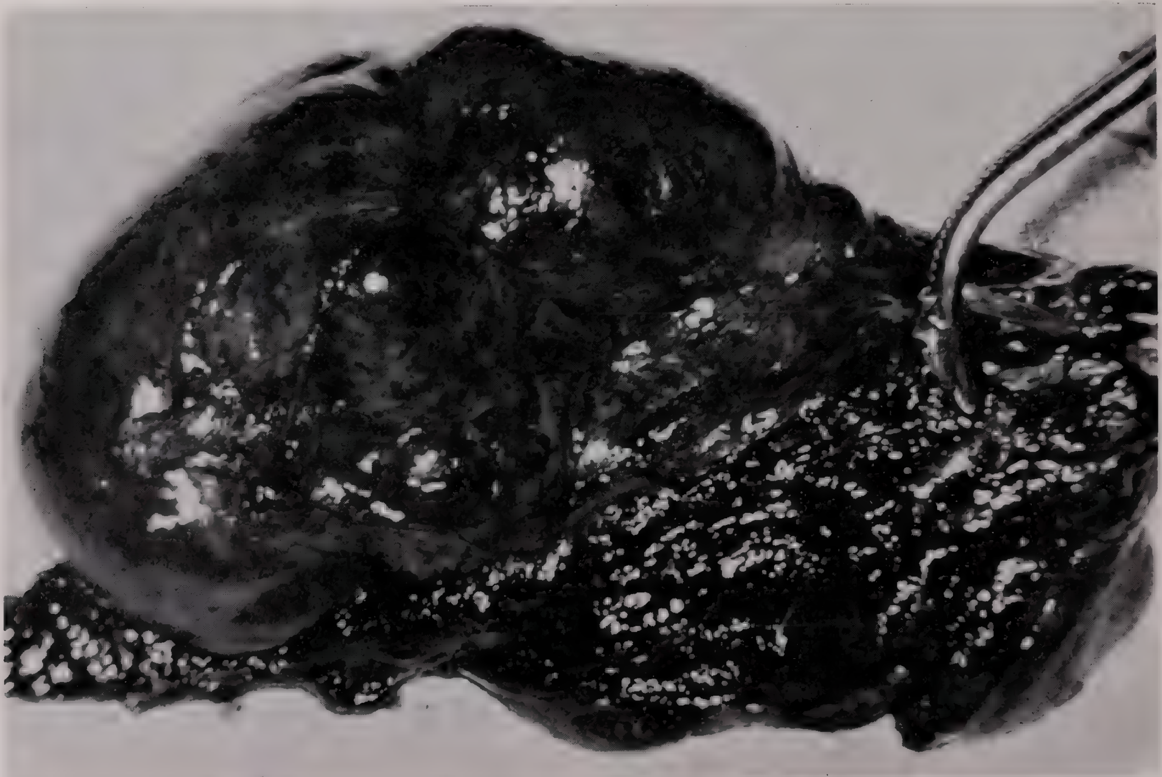

Fig. 3 — Apical and posterior segments of the right upper lobe of patient #16, which are atelectatic while gas remains trapped in the surface cyst.

function did not necessarily improve after segmental resection or lobectomy, although all patients except #16 had preoperative pulmonary functions of 75% or more than predicted.

Discussion

Bullous emphysema has been termed the "vanishing lung" syndrome[1] inasmuch as the natural history of an acquired air cyst is one of expansion. Because gas flow is into the cyst alone, it has been noted to expand on coughing and expiration.[4] As the cyst grows, the functional parenchyma vanishes as it becomes compressed and atelectatic.

Although a pathologic distinction is made

TABLE 2

	1 sec. Vital Capacity		Total Vital Capacity		Maximum Breathing Capacity	
	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.
Vital Capacity 75% or less than predicted						
1. 1st operation	1.9	2.7	3.1	3.5	90	109
2.	1.7	2.7	2.7	3.5	—	98
3.	1.7	2.2	2.3	3.3	—	86
4. 1st operation	0.4	—	1.0	—		
4. 2nd operation		1.7	—	2.2	—	71
5.	1.5	1.6	2.3	2.9	—	69
6.	1.4	1.7	1.9	2.9	49	72
7.	1.0	1.1	1.8	2.8	40	41
8.	1.0	0.8	2.6	2.1	53	50
9.	1.2	1.2	2.3	2.0	31	35
10. 2nd operation	1.7	1.2	2.7	2.3	85	105
Vital Capacity 76% or more than predicted						
1. 2nd operation	2.7	2.9	3.5	3.2	109	118
11.	2.5	2.6	3.4	3.5	89	107
12.	2.6	2.6	3.6	3.3	97	114
13.	2.0	2.0	3.8	3.8	—	57
14.	1.5	1.5	2.9	3.5	52	55
15.	2.5	3.2	4.2	3.3	102	86

Pre and postoperative pulmonary functions in 15 patients who had only removal of cystic spaces and obliteration of the pleural space. The patients are listed in two groups according to preoperative vital capacity.

TABLE 3

	1 sec. Vital Capacity		Total Vital Capacity		Maximum Breathing Capacity	
	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.
Segmentectomy						
16.	1.2	1.3	2.8	3.3	51	57
17.	3.2	2.7	4.4	4.1	160	118
18.	2.7	2.2	4.0	4.1	106	99
10. 1st operation	1.5	1.7	3.2	2.7	77	85
19. 2nd operation	2.8	2.8	4.0	4.1	99	82
Lobectomy						
20.	1.1	1.0	3.1	2.5	38	43
21.	2.9	2.1	4.1	3.5	114	99
22.	1.9	2.1	3.4	3.1	64	83
23.			3.0	3.2		
19. 1st operation	3.5	2.8	5.8	4.0	113	99

Pre and postoperative pulmonary functions in patients who had segmentectomy or lobectomy to remove their air spaces.

between bullae and giant blebs,[6] they both cause the same symptoms and secondary complications, and are therefore clinically indistinguishable. For practical purposes one can consider both bullae and blebs as acquired lung cysts.

The etiology of these cysts is unknown, although they appear to be associated with partial expiratory obstruction. Many of these patients have asthma, chronic bronchitis and generalized pulmonary emphysema. However, the average age of these patients is younger than that of symptomatic generalized emphysema.[7]

The symptoms and secondary complications of these cysts are due to the mechanics of a space-occupying mass. If the visceral pleura overlying a cyst ruptures, air leaks into the pleural space resulting in pneumothorax. This was the most frequent reason for hospital admission in this series. Atelectasis predisposes to pneumonitis, which was also a common recurrent finding.

Postoperatively in patients whose pleural space had been obliterated, these complications have not been noted, nor has there been a recurrence of the air spaces. Even when pulmonary function is not improved, surgery will make recurrent pneumonitis less likely, prevent pneumothorax, and curtail further enlargement of small blebs.[5]

Infection within the cyst is an infrequent finding.[7] Active tuberculosis and bronchogenic cancer have been reported as causative factors.[10,11] Of the five patients in our series who had fluid levels within the air spaces there were two proven cases of tuberculosis and one probable case.

Improvement in pulmonary ventilation and oxygen diffusion following surgery has been well documented.[2,3,9,12] If total vital capacity before surgery was depressed 25% or more and only the cysts were removed, one could expect significant increase in pulmonary function postoperatively, even though most of these patients had generalized emphysema as well. Ogilvie and Catterall[9] found postoperative improvement in patients whose air space occupied 50% or more of the hemithorax, whereas removal of small cysts did not necessarily result in better ventilation. Preoperative reduction in pulmonary function is not a contraindication for surgery when one can expect improvement with excision of the cysts.

Patients who had segmentectomy or lobectomy had a variable response to surgery, although as a group, preoperative pulmonary functions were not markedly depressed. In all instances pulmonary tissue capable of function was removed. These patients probably would have been better served had only the walls of the air spaces been removed.

Summary and Conclusion

Poor pulmonary function is not a contraindication for surgery if associated with giant bullae and/or pneumothorax.

Because giant air spaces are anatomically on the lung surface, one need not remove the lobe or lung segment.

Obliteration of the pleural space prevents pneumothorax and small bullae or blebs from expanding.

When giant bullae are found to contain fluid, one should suspect active tuberculosis.

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Monkey: an arboreal animal which makes itself at home in genealogical trees.

— Ambrose Bierce

Cerebral Vasospasm

1965*

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PRIOR TO 1950, recurring, intermittent attacks of cerebral dysfunction, frequently reversible, were thought due to focal spasm of the cerebral blood vessels. This view was succeeded by the concept of cerebrovascular insufficiency when increasing angiographic evidence of vascular occlusion and stenosis was developed. Denny-Brown, in 1951, described carotid and/or basilar insufficiency as a physiological, potential hemodynamic state, in which reversible hemodynamic crises could be elicited by any factor that impaired collateral circulation.[2]

Cerebral angiography increased its scope, demonstrating more areas of organic occlusion and stenosis. Surgical techniques were developed in order that these areas could be improved or repaired. A concept of vasospasm as a etiologic factor in the production of stroke and the treatments directed toward its alleviation disappeared almost completely; stellate ganglion block and cerebral vasodilators fell into disuse.

The concept of cerebral vasospasm was not completely lost however. Direct microscopic study of the pial vasculature by means of the Forbes window and modifications was carried out by many investigators.[5,7] There is no longer any question that the cerebral blood vessels, particularly the larger vessels about the base, respond actively to mechanical stimulation. Chemical, hormonal and metabolic stimuli are likewise effective in producing constriction and dilations.[12] The mechanism by which this vasomotor control is exerted appears similar to that responsible for vasomotor changes elsewhere in the body. Although reactive vasospasm has been the subject of many reports, the responsible mechanisms are not entirely understood.

The subject of cerebral vasospasm in relation to subarachnoid hemorrhage of ruptured aneurysm continues to attract considerable attention.[1] The mechanism of this angiospasm, sometimes local in the area of the ruptured aneurysm, sometimes general throughout the cerebral circulation, and occasionally distant from the site of rupture, has been the topic of many reports.[8] No clear mechanism has been demonstrated.

Vasoconstricting Drugs

Serotonin, angiotensin and barium chloride have been shown to produce vasoconstriction when applied to the pial vessels topically.[9] When applied in a similar manner, these same drugs will cause constriction of the major cerebral vessels about the base. The vasoconstrictor effect of these drugs has been demonstrated in the mouse, the cat and the monkey. Angiotensin has been shown to have a similar effect on the exposed pial vessels of the human.[12,13] Recent work by Ecklin, reported in New York, April, 1965, has demonstrated local vasospasm due to application of blood. Other investigators have not yet been able to reproduce this work.

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Vasodilating Drugs

Inasmuch as nylidrin hydrochloride, isoxsuprine hydrochloride and papaverine are known to have vasodilating potential, these drugs were studied in topical application to the pia. All three drugs produce definite and clear vasodilation. Of the three, papaverine appears most effective. Attempts to produce vasodilation of the cerebral vessels by the intravenous administration of these compounds were somewhat more difficult. Isoxsuprine hydrochloride and nylidrin hydrochloride failed to produce demonstrable cerebral vasodilation, as determined by continuous cinemicrophotographic study, in our laboratory, even when given in doses massive enough to cause lowering of the blood pressure from generalized vasodilatation. Papaverine, on the other hand, produced vasodilatation when given intravenously. If given in large enough amounts this drug would also produce a shock state in the animal.

Attempts to block the vasoconstricting effect of barium chloride were next evaluated. Rosenbloom and Zweifach[10] were able to demonstrate reduction in the vasoconstriction caused by barium chloride if the application followed the topical use of nylidrin hydrochloride.

Method

A group comprising 25 cats and 12 monkeys were studied for the effect of topically applied vasoconstricting and vasodilating compounds. An additional five cats were utilized to study the effect of intravenous vasodilating compounds. The animals were anesthetized with phenobarbital anesthesia and the experiments were photographically recorded on 16 millimeter Kodachrome film at a four-fold magnification. Five per cent barium chloride, 0.01% serotonin and 0.05% angiotensin were used in topical application to produce vasoconstriction. These drugs were gently flowed onto the exposed pial while the vessels under study were continuously observed and recorded. Five tenths of one per cent of isoxsuprine hydrochloride and 0.5% nylidrin hydrochloride were used as topical application for vasodilation. Three per cent papaverine was used in a similar fashion.

Results

Species variation and reactivity, as reported earlier by Lende[7] and Ecklin,[3] were ap-

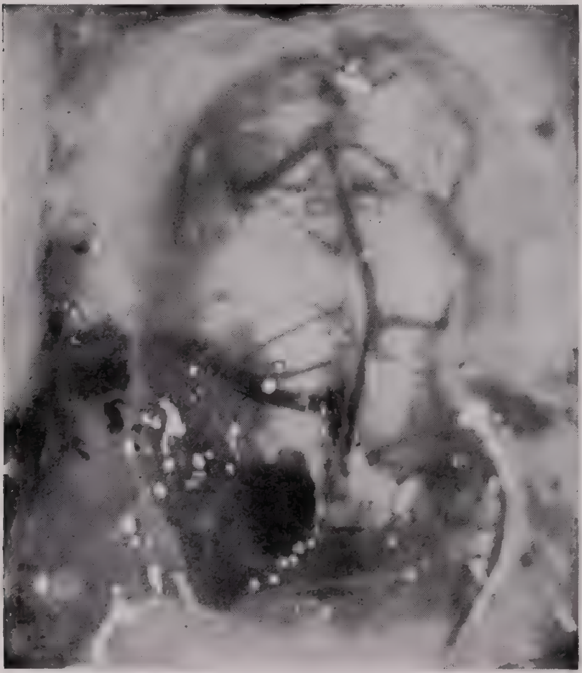

Fig. 1a — Normal basilar artery in the cat.

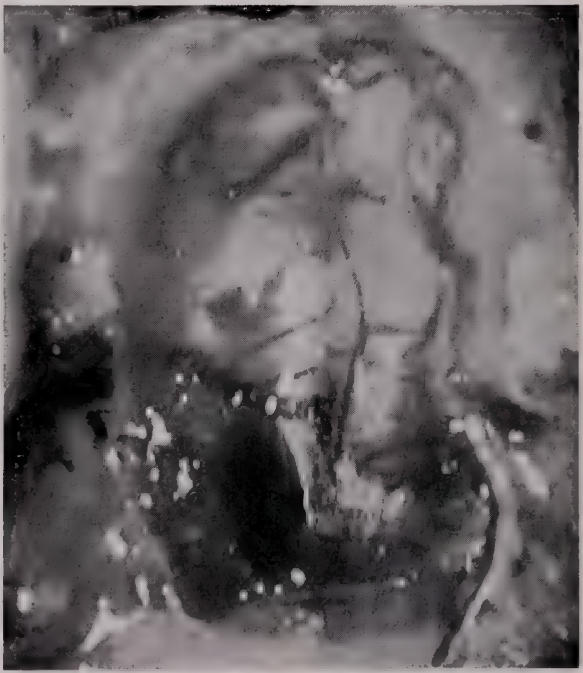

Fig. 1b — Vasoconstriction of basilar artery from 5% barium chloride.

parent. The blood vessels of the cat seemed the most reactive. Those of the monkey and human appeared to react in a similar fashion, the monkey possibly somewhat more actively. Topically applied 5% barium chloride was a potent vasoconstricting agent and resulted in marked vasoconstriction more than 80% of the time. Serotonin was nearly as effective and angiotensin appeared the least powerful. Isoxsuprine hydrochloride and nylidrin hydrochloride each produced vasodilation when applied topically. The same was true of papaverine.

When topical applications of barium chloride and isoxsuprine hydrochloride were alternated, each would counteract the other's effect and produce its own characteristic results. In the experiments related in this paper no demonstrable blocking of either substance by its opponent could be demonstrated.

Intravenous isoxsuprine hydrochloride failed to produce vasodilatation. When topical barium chloride was applied during the continuous intravenous use of isoxsuprine, vasoconstriction readily occurred.

Topically applied papaverine produced vasodilation, and this same result can be obtained with the intravenous use of papaverine. Again no blocking effect to the vasoconstricting action of topically applied drugs was noted.

Discussion

The vasomotor reaction of the cerebral blood vessels to physical, metabolic and chemical stimuli is now well documented. Reaction of the pial vessels to smooth muscle activators has been demonstrated. The pial blood vessels respond by dilation to the use of smooth muscle relaxant drugs such as isoxsuprine, nylidrin and papaverine. Although others have demonstrated a blocking effect of nylidrin hydrochloride we have, as yet, been unable to reproduce these results.

It is not clear whether the intravenous use of papaverine or similar compounds will reverse the vasospasm produced in certain cases of subarachnoid hemorrhage. It is, at this time, not possible to produce vasospasm artificially by subarachnoid hemorrhage. Recent work by Ecklin suggests that application of blood directly to the larger vessels about the base will produce definite vasospasm. Unfortunately, under the circumstances, the vasospasm does not persist for more than a

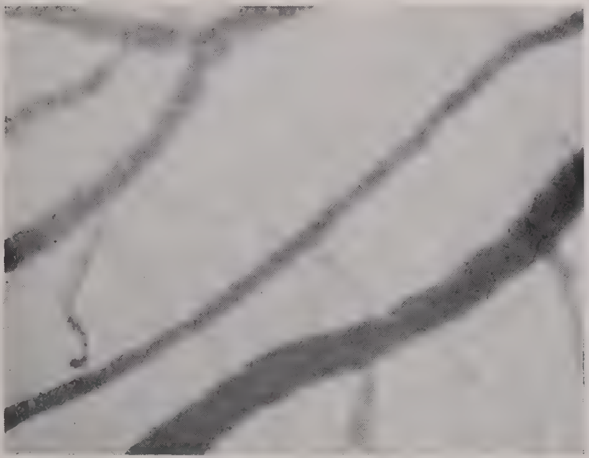
Fig. 2a — Pial vessel of 100 micra constricted by barium chloride.

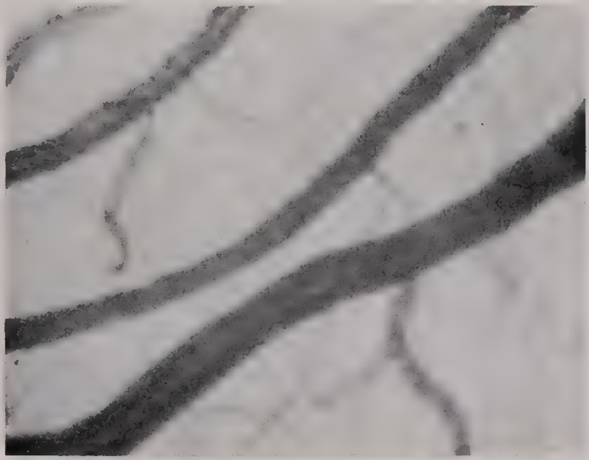
Fig. 2b — Same vessel dilated by intravenous papaverine.

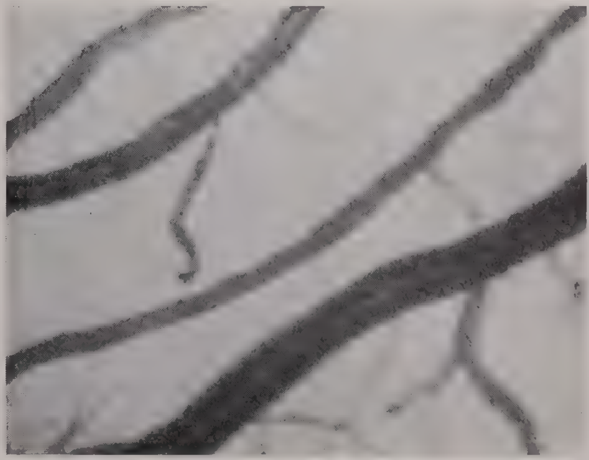
Fig. 2c — Constriction by barium chloride in spite of continous intravenous papaverine.

few minutes. Presumably such studies will require careful clinical evaluation and the use of repeated angiographic studies. It is not entirely clear whether or not the relief of the vasospasm following subarachnoid hemorrhage might result in further bleeding. Presumably this would be safe enough 12 to 24 hours after the bleed, by which time the clot should be firmly established in the rupture site.

Summary

Although cerebral vasospasm is no longer considered a cause of intermittent attacks of paralysis, weakness or dysphasia in the stroke syndrome, the effect of vasospasm in subarachnoid hemorrhage is well documented. Studies relating to cerebrovascular constricting and dilating substances have shown that barium chloride, serotonin and angiotensin produce vasoconstriction when applied topically. Nylidrin, isoxsuprine and papaverine produce vasodilation. None appears to block the effect of its opponent. Papaverine is alone in producing vasodilatation when given intravenously.

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The Common People

The genius of the United States is not best illustrated in its executives or legislators, nor its ambassadors or authors or colleges or churches or parlors, or even in its newspapers or inventors — but always most in the common people. Their manners, speech, dress, friendship — the freshness and candor of their physiognomy — picturesque looseness of their carriage . . . their deathless attachment to freedom — their aversion to anything indecorous or soft or mean — the practical acknowledgment of the citizens of one state by the citizens of all other states — the fierceness of their roused resentment — their curiosity and welcome of novelty — their self esteem and wonderful sympathy — their susceptibility to a slight — the air they have of persons who never knew how it felt to stand in the presence of superiors — the fluency of their speech — the delight in music, pure symptom of manly tenderness and native elegance of soul . . . their good temper and open handedness — the terrible significance of their elections — the president's taking his hat off to them, not them to him — these are unrhymed poetry. It awaits the gigantic and generous treatment worthy of it. — Walt Whitman Leaves of Grass 1855

Iron Deficiency Anemia as Related to Zinc*

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IRON-DEFICIENCY anemia is a major health problem in developing countries.[1] Poor dietary intake and/or availability of iron, blood loss caused by parasites, loss of iron by excessive sweating, and geophagia† in some cases are possible reasons for iron deficiency in many countries.

Dietary Deficiency

In Iranian villages the diet consists mainly of bread made of wheat flour, with practically no intake of any animal protein, fruits or vegetables. In addition, several patients consume large quanties of clay (geophagia). It is believed that the predominantly high cereal content of the diet and geophagia, by virtue of their increased phytate and phosphate content, make the dietary iron unavailable for absorption.[2-5] Hookworm infection, which can cause excessive blood loss, is a common occurrence in the delta villages of Egypt. Loss of iron by sweating is not an important factor for persons living in temperate climates[6] but could account for at least 1 to 2 mg. of iron loss per day in normal subjects by excessive sweating in a hot climate.[7] Thus a combination of the above mentioned factors in addition to low intake of iron is responsible for high incidence of iron-deficiency anemia in developing countries.

Effect on Tissues

Tissue effects of iron deficiency in animals and human subjects have been well described.[8,9] Iron-deficient New Hampshire

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†See Test Your Word Score Page 97.

chicks have white feathers instead of their normally reddish-brown plumage. The iron-deficient rat loses the deep orange pigment of its incisors; a decrease in gastric-acid secretion and an increase in the size of the caecum have been noted in rats given an iron-poor diet. The inability to absorb vitamin B_{12} by iron-deficient rats, perhaps caused by defective intrinsic factor secretion, has also been described. Rats and elephants continue to grow on iron-deficient diets and develop marked anemia during the period of rapid growth.[10]

In human subjects, iron deficiency causes changes in the mucosa of the alimentary tract.[8,11] The oral mucosal epithelium is abnormally thin in some patients. Mitoses in the prickle-cell layer are more frequent in iron-deficient than in normal subjects. Melanin deposition is less, and subepithelial inflammation is increased.

Clinical Manifestations

Changes in the esophagus of iron-deficient patients give rise to "sideropenic dysphagia."* Constrictions or webs of the hypopharynx or esophagus result in inability to swallow solid food.[12] Histopathologic findings have included keratinization of the lingual epithelium and leucocytic infiltration of the submucosa. Atrophy, hyperkeratinization and changes resembling leukoplakia have been described in the esophageal mucosa. The esophageal lesions of iron deficiency have been regarded as precancerous.

Gastric atrophy and achlorhydria are commonly associated with this disorder.[13] Changes vary from superficial to atrophic gastritis. It is unclear whether these are the results of iron deficiency or whether they are of etiologic significance in development of hyposideraemia.

In blood, unrelated to decreased hemoglobin synthesis, one may find leukopenia, thrombocytopenia and a poorly defined bleeding tendency.[14]

Koilonychia* has been observed in iron deficiency. It has been suggested that a dietary cystine deficiency may be important in the development of this abnormality.[8]

A large number of individuals in Egypt have low serum iron, high unsaturated iron-binding capacity and low normal hemoglobin level. Similarly, patients with iron-deficiency anemia would recover promptly within three to four weeks of iron therapy so far as the hemoglobin and hematocrit were concerned, but their serum iron would remain essentially unchanged for several weeks in spite of therapy.[3] This emphasizes that in a population where the nutrition with respect to iron is basically inadequate, a near normal hemoglobin level does not indicate normal tissue iron saturation as judged by serum iron and unsaturated iron-binding capacity determinations. These subjects, however, develop marked anemia due to added blood loss when they get infected with hookworm.

Zinc-Deficiency Syndrome

Zinc is an essential nutrient factor for both plants and animals. Its essentiality for growth in plants was established in 1926; in 1934 it was first demonstrated that zinc was essential for growth in the rat. The clinical features of zinc deficiency in rats were first described in 1941, in pigs in 1955 and in poultry in 1958.[15]

Clinical Manifestations

During our studies in Shiraz, Iran, we encountered a group of adult males who presented the following clinical picture: severe iron-deficiency anemia, hepatosplenomegaly, hypogonadism, dwarfism and geophagia. Their diet consisted mainly of bread made of wheat flour with practically no intake of animal protein. These patients showed no blood loss and no evidence of malabsorption.[2]

Since iron deficiency alone does not produce retarded growth and sexual hypofunction, it appeared likely that other associated deficiencies may have been operating. The content of iron and zinc in most foodstuffs parallel each other; both metals are complexed with phosphates and phytates, thus making them unavailable for absorption. Both are present in high concentration in red cells. Therefore in chronic blood loss one may expect both deficiencies. Sweat excretion in tropical climate may account for 1-2 mg. of zinc loss per day, similar to that of iron loss.[7] Furthermore, the growth failure and testicular changes observed in these dwarfs appeared very similar to those encountered in zinc-deficient animals.

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*See Test Your Word Score Page 97.

Subsequently our studies in Egypt indicated that similar subjects with identical clinical features were zinc-deficient.[3,4] Seventeen such patients who came from the delta villages near Cairo, Egypt, were studied in detail. Clinically they showed the same features as previously described for Iranian patients; their growth was retarded, and all had hypogonadism, hepatosplenomegaly and iron-deficiency anemia. Their diet consisted mainly of bread and beans (vicia fava), with negligible intake of animal protein. They differed from the Iranian group in that they all had schistosomiasis and hookworm infections; but geophagia was not observed.

Nutritional zinc deficiency in human subjects had not been recognized prior to our observations. In patients with liver cirrhosis, hyperzincuria is present, resulting in decreased levels of zinc in the plasma and the tissues.[15] Our subjects in Iran and Egypt had no evidence of cirrhosis of the liver.[18] The Egyptian subjects had granulomas in the liver due to schistosomiasis but did not have portal cirrhosis. Their liver-function tests were unremarkable except for the changes in the serum alkaline phosphatase, to be discussed later and their excretion of zinc in the urine was less than in normals. Thus we concluded that in our cases liver disease was not a factor in the production of zinc deficiency.

Metabolic Studies

Zinc metabolism studies in these subjects indicated that zinc content of plasma, red blood cells and hairs were reduced as compared to the normals (Table 1). Zinc-65 studies revealed a decreased plasma disappearance rate in the initial phases, a rapid

TABLE 1
Summary of Trace Metals Data in Normals and Dwarfs

	Normals	Dwarfs	Comparison of Means
1. Plasma zinc in μg %.	102 ± 13.0	67 ± 11.0	$P < .01$
2. RBC zinc in μg per ml.	12.5 ± 1.2	9.7 ± 1.1	$P < .01$
3. Hair zinc in parts per million.	105 — 136	30 — 75	——
4. Plasma copper in μg %.	125 ± 22	142 ± 24	$P < .05$
5. Serum iron in μg %.	87 ± 14	35 ± 14	$P < .01$
6. Plasma magnesium in mEq per liter.	1.90 ± 0.19	1.82 ± 0.12	Not significant

TABLE 2
Summary of Zn^{65} Studies

	Normals	Dwarfs	Comparison of Means
1. Plasma zinc turnover rate in mg/kg/day.	1.00 ± 0.09	1.50 ± 0.29	$P < .01$
2. 24 hour exchangeable zinc pool in mg/kg.	7.00 ± 1.6	4.6 ± 1.2	$P < .01$
3. Excretion of Zn^{65} per 100 gm. of stool in % of dose administered.	0.66 ± 0.19	0.42 ± 0.13	$P < .05$
4. Excretion of Zn^{65} in urine in 13 days in % of dose administered.	2.80 ± 0.56	1.60 ± 0.68	$P < .01$

turnover rate, and a decreased 24-hour exchangeable zinc pool in the dwarfs as compared to the normals (Table 2). The excretion of Zinc-65 in urine and stool was less in the dwarfs. All these data were considered as evidences of zinc deficiency in this group of subjects.

Treatment

In every case, following adequate treatment, the serum alkaline phosphatase increased markedly. Similar phenomena in zinc-deficient animals after treatment have been reported.[19] Alkaline phosphatase is a zinc-containing enzyme. The increased activity of this enzyme following treatment may possibly be the result of increased availability of zinc for its synthesis. Alkaline phosphatase increases with increased growth hormone levels. Thus the increasing level of this enzyme may be indicative of increased production of growth hormone following treatment.

Diet and Iron

The Iranian patients were treated with oral ferrous sulfate and good hospital diet. Their hemoglobin became normal within six to eight weeks. The size of the liver and spleen decreased, and pubic hair appeared with an increase in growth. Three of the patients who were followed after a year had developed a normal growth pattern and had normal sexual development. However, since commercial iron preparations contain appreciable amounts of zinc, one could not be certain if these manifestations were being reversed because of the iron or the zinc administration.

Experimental Treatment

To establish a relationship further, the Egyptian patients were kept on wards of U. S. Naval Medical Research Unit No. 3 in Cairo for prolonged periods of observation under treatment with reagent grade pure iron or zinc. Careful measurements of their height along with their clinical, hematological and biochemical status were determined at suitable intervals.

Adequate Protein and Calories

Two subjects were kept on good diet (adequate in animal protein and calories) for 12 weeks but received no supplemental iron or zinc. Both gained one inch in height during this period, and their plasma zinc increased significantly.

Adequate Diet and Iron

At the end of this period, one of them was started on iron and the other received zinc. The patient on iron grew one inch in 14 weeks, whereas the one on zinc grew one inch in 10 weeks. Another patient received iron for 16 weeks without any change in height, and the third patient on iron gained 1¼ inches in 24 weeks. The size of the genitalia remained unchanged, and no growth in pubic hair occurred in patients receiving iron treatment; but their anemia was fully corrected.

Adequate Diet and Zinc

On the other hand two other patients on zinc gained 1 and 1.6 inches in height during seven weeks, whereas a third gained 2 inches in 10 weeks of zinc therapy. All four subjects on zinc showed a remarkable increase in size of their external genitalia and grew dark pubic hairs during the period of observation; but they remained anemic. The majority of the patients had roughened hyperpigmented skin mainly in exposed areas, which promptly cleared following treatment with zinc supplement and good diet. The excretion of follicular stimulating hormone in urine increased remarkably following zinc treatment. In addition serum alkaline phosphatase increased, and hepatosplenomegaly became less prominent in patients receiving zinc as compared to those on iron. Thus, under the conditions of our experiments, the rate of growth was greater, the genitalia size increased, and pubic hairs appeared in patients who were treated with zinc as compared to those who received iron treatment.

Vitamins and Other Trace Elements

Serum levels of Vitamin B_{12}, C and A were normal. No evidence of folic acid or B_6 deficiency was obtained as determined by the formiminoglutamic-acid and xanthurenic-acid excretion tests.[3] Copper level in serum was slightly increased, and serum magnesium was normal.

Zinc Deficiency

Thus our detailed investigations revealed that two factors were complicating the clinical features in these subjects: the first, iron-deficiency anemia, and the second, zinc deficiency. The possibility that severe anemia alone could account for the retardation of growth and hypogonadism was considered. However, our studies in Kharge oasis indicated that a group of patients with this syndrome were only mildly anemic because they had no blood loss due to parasitic infestation, but their serum zinc levels were decreased, thus indicating that anemia alone was not a factor in affecting the growth and gonadal development.[5] Growth retardation and sexual hypofunction do not occur in experimental iron-deficient animals. On the other hand these features are constantly observed in animals made zinc-deficient.

Hypogonadism

I appears therefore that zinc deficiency in these human subjects was probably responsible for growth retardation and hypogonadism.

Hormone Deficit

In all our patients in Egypt the urinary 17 hydroxycorticoids were low normal, but 17 ketosteroids excretions were decreased. Follicular stimulating hormone excretion in urine was low in all cases. In some patients the endogenous production of adrenocorticotropic hormone was decreased.[20] Thus pituitary hypofunction was evident with respect to growth hormone, gonadotropic and adrenocorticotropic hormone activities. Serum protein-bound iodine was normal, indicating normal thyrotropic activity.

Comments

Since the investigations on the patients with hypogonadism and dwarfism suggest that zinc plays a highly significant role in human nutrition, and since zinc deficiency in plants and animals has been well documented, it appears reasonable to predict that certain poorly understood clinical disorders in man, not yet recognized as being related to abnormalities of zinc metabolism, may actually be so related.

For example, koilonychia, considered to be a cardinal sign of chronic iron deficiency, has been noted in experimental zinc deficiency in animals. Likewise esophageal changes occur in these animals. It is possible therefore, that the esophageal "web" of the Plummer-Vinson syndrome* may actually be a manifestation of associated zinc deficiency.

Thus it is timely to re-evaluate some of the manifestations of chronic iron deficiency as being possibly related to associated zinc deficiency. When we consider the close similarity between iron and zinc in relation to such features as body content, serum and red-cell concentration, and possible absorption mechanisms, this relationship becomes a significant possibility. However, this must be considered speculative until further research provides answers.

It is evident, then, that in patients with nutritional iron-deficiency anemia, one must also look for associated zinc deficiency. A recognition of this association will stimulate further research in this area, which will ultimately clarify specific tissue effects of iron and zinc deficiencies. Even in animal experiments, critical studies to differentiate tissue effects of iron deficiency are lacking, and one must therefore evaluate results accordingly.

Our patients in the Middle East consumed a high cereal diet. According to our analysis a sample of Iranian wheat contained 0.66% of phytate; seventy-one per cent of the total phosphorus in this wheat was phytate phosphorus. Presence of phytate makes zinc less available for absorption;[21,22] therefore we believe that high phytate content in the diet must be a major factor in production of this deficiency.

We obtained no evidence for copper deficiency in our patients. This would indicate that copper was adequate and available in their diet. Copper and manganese are present in large quantities in cereals, and the effects of phytate on these trace metals are not nearly as pronounced as in the case of zinc.[23] Furthermore, our patients did not present any clinical similarities to those in animals suffering from these deficiencies.

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*See Plummer-Vinson Syndrome Page 64.

We did not measure serum cobalt in our patients. However, the anemia in all patients responded to iron administration only. Furthermore, the severe emaciation evident in cobalt-deficient animals was not noticed in our subjects.

It is clear that more work needs to be done in order to define availability of these trace metals in diets normally consumed. Some studies concerning this problem are presently in progress in Egypt.

Summary

A group of patients from the Middle East, exhibiting iron-deficiency anemia, hepatosplenomegaly, dwarfism and hypogonadism, were studied extensively and found to have zinc deficiency as well as iron deficiency. This is the first description of nutritional zinc deficiency in human subjects. Our studies strongly suggest that dietary zinc deficiency in man can cause extreme retardation of growth and of gonadal development.

In Shiraz, Iran, severe iron-deficiency anemia was encountered in adults in the absence of any blood loss and/or malabsorption syndrome, thus indicating that their cereal diet and geophagia most likely made the iron unavailable for absorption.

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5-23 May be secured from the author or the reprints.

PLUMMER-VINSON SYNDROME

Dysphagia, atrophic changes in the buccal, glossopharyngeal, and esophageal mucous membranes, spoon-shaped nails, and a microcytic, hypochromic anemia are the characteristic features of this syndrome, first described by Plummer in 1914. It occurs predominantly in middle-aged women.

Anemia is usually present and sideropenia is normally found. There may be a dry mouth and pharynx and a sensation of nasal obstruction, evident for a number of years before the onset of the anemia.

Dysphagia is a conspicuous symptom. There may be associated stomatitis, glossitis, cheilitis, hypochlorhydria or achlorhydria, splenomegaly, and spoon-shaped brittle nails. A weblike filling defect at the upper end of the esophagus has been observed, which disappears after therapy.

There is a tendency for these patients to develop oral pharyngeal cancer.

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You never get ahead of anyone as long as you are trying to get even with him.

Neonatal Gastric Rupture

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SPONTANEOUS GASTRIC rupture in the newborn has until recently been considered a rare condition. However, it is the most common of visceral perforations in infants, and a total of 168 cases with 43 survivals have now been reported. The purpose of this report is to document a recent case, point out the diagnostic features and describe the pathology. In addition, a mechanism responsible for this phenomenon based on experimental work in dogs is proposed.

Case Report

This 5-pound white female infant was born November 30, 1961, following a 38-week gestation. Delivery was somewhat difficult as a result of a compound presentation. However, there was no evidence of fetal hypoxia. The baby did well for three days and passed meconium stool. However, on December 3, 1961 (approximately 68 hours after birth), she developed abdominal distention, failed to take food, vomited and became lethargic.

Physical Findings

Examination of the heart and lungs was noncontributory, but there was moderate respiratory distress which appeared to be secondary to the abdominal distention. The abdomen was resonant to percussion; there were no bowel sounds. There was edema of the parietes. Rectal examination was normal. Hemoglobin was 17.5 grams per cent and white blood count 2,150 per cubic mm. Roentgenograms of the abdomen showed pneumoperitoneum (Figure 1). The diagnosis of a ruptured hollow viscus was made and the infant taken to the operating room.

Operative Findings

A catheter was placed in the saphenous vein at the ankle and exploratory laparotomy carried out under general anesthesia. A longitudinal tear of the anterior wall of the stomach was seen. It measured 7 cm. in length, involved the fundus and body and extended to the antrum. A narrow margin about the gastric defect was necrotic. A whitish and somewhat adherent material which appeared to be infant for-

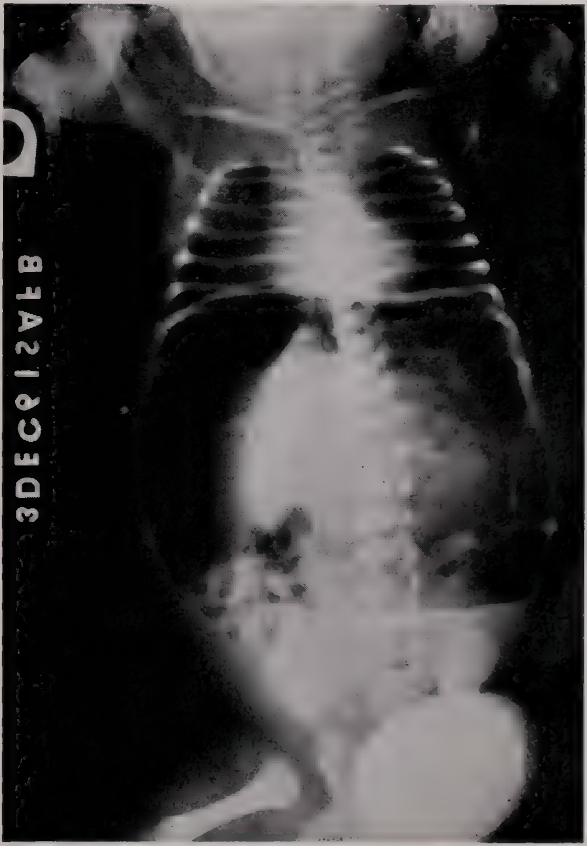

Fig. 1 — Upright roentgenogram. Note the "saddle bag" configuration of the air density.

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mula coated both the visceral and parietal peritoneums. This material was picked off. There appeared to be an early generalized peritonitis. Debridement of the lacerated margin was then carried out and the gastric defect repaired with a 2-layer closure. (Microscopic section of material excised from the margin showed acute inflammation and amorphous debris.) Following closure, the stomach was reduced in size and had a tubular appearance. The peritoneal cavity was thoroughly irrigated with saline and the abdominal wall closed. No drains were placed. The patient's postoperative course was uneventful. When seen three years later, she was a bright little girl with normal growth and development.

Comments

A ruptured hollow viscus should be suspected in the newborn with the clinical picture described.

Pneumoperitoneum

Gastrointestinal dilatation also causes abdominal distention, but pneumoperitoneum seen on upright abdominal roentgenogram confirms the diagnosis of visceral disruption. It is not possible to localize the ruptured viscus with absolute certainty in any particular case. However, an impressively constant picture is seen when gastric disruption occurs in neonatal life. This patient conforms to the pattern generally described for this entity, except for the sex incidence in which males predominate with a ratio of 1.5 to 1.0.

Prematurity

Characteristically, these infants who may be premature do well for two to four days following birth. They take feedings and pass normal stool.

Sudden Onset

Then there is a sudden onset of lassitude, abdominal distention, and dyspnea, followed by paralytic ileus, dehydration and shock. Massive pneumoperitoneum is seen by x-ray. In the upright film, the striking appearance of the air outline has been called the *saddlebag* configuration.[1] Studies with barium or other radiopaque media should not be done. Since they are not necessary for diagnosis, they delay treatment and add more foreign material to the peritoneal cavity. The evidence of a visceral perforation within the first four days of life in a newborn who had been doing well should lead to a presumptive diagnosis of gastric rupture. More distal visceral perforations *usually* occur in older infants. Also, gastric rupture is more likely to occur on a statistical basis, since all reported disruptions of the duodenum, remaining small bowel, and colon in the newborn total less than the number of gastric disruptions.[2]

Treatment

Treatment for rupture of any hollow viscus in the newborn is the same, and except for placement of the incision, preoperative localization of the perforation site is not essential. Intravenous fluids, gastric suction, and antibiotics should be started at once and laparotomy performed. Surgical closure of the perforation is then carried out, since the omentum in the newborn is small and thin and unlikely to seal any perforation. A careful inspection of the viscera should be made, because multiple perforations have been described. It is not necessary to drain the peritoneal cavity.

Several cases of pneumoperitoneum have been described where the source of free air could not be identified.[3] The term "spontaneous pneumoperitoneum of the newborn" has been suggested for this entity. The few infants who have survived pneumoperitoneum without operation probably belonged in this category.

Only 10 cases of gastric disruption were reported in the century following the first description of the entity in 1825.[4] However, within the past 15 years a considerable number have appeared in the world literature. An attempt at closure of a perforated stomach in infancy was made by Stern[5] in 1929. Leger,[6] who operated and reported on his case in 1950, is credited with the first successful repair. Ross[7] and Kellogg,[8] at about the same time, described operative treatment with survival.

Etiology

The etiology of spontaneous gastric rupture in the newborn is not known, although a number of causes have been proposed.

Peptic Ulcer

Until several years ago, most gastric disruptions were assumed to be due to peptic ulcer, although Herbut[9] in 1943 had already described a congenital defect in the muscle of the stomach wall in some of these cases.

Most gastric disruptions in the newborn have the appearance of a long linear and ragged rupture or laceration rather than a perforation, and most occur on the fundus or greater curvature. A "punched out" type of lesion is less frequently seen, and even these do not show the intensely acute and chronic inflammation characteristic of peptic-ulcer perforations.

Distal Obstruction

Distal obstruction has been present in several cases and various congenital anomalies have been described, but there is no predominant associated defect. Gastric disruption may occur with duodenal atresia, although this is uncommon. It has not been reported with hypertrophic pyloric stenosis. Ruptured gastric diverticula have been described in a few cases.

Trauma

A number of cases of gastric trauma and perforation have been described. Most of these were the result of intubation with a staff catheter, or air-oxygen administered under pressure by means of a face mask. This group of perforations should not be called "spontaneous." Lloyd[2] has recently implicated fetal anoxia as an etiologic factor.

These studies were stimulated because the gastric disruption in this case and in most of the other cases reported[1] appears comparable morphologically to a distention-bursting type tear. Most of these disruptions occur in the fundus or on the greater curvature which has lower local bursting strength than the lesser curvature or antrum-pyloric area during the first decade of life.[10]

Experimental Studies

In 10 dogs the esophagus and stomach were removed and a tube inserted into the stomach via the esophagus. The pylorus and distal esophagus were ligated. Pressure within the stomach was monitored as the stomach was distended with air or water. In the remaining dogs, esophagus and stomach were left in situ, and celiotomy was done to ligate the pylorus and distal esophagus. The abdominal wall was left open in 21 dogs and closed in 72. A mean intraluminal pressure of 142 mm. Hg. caused rupture of the stomach when isolated, or when the abdominal wall incision remained open and there was no impeding of the huge dilation. With the stomach expansion limited by closure of the abdominal incision, a mean 196-mm. Hg. caused rupture.

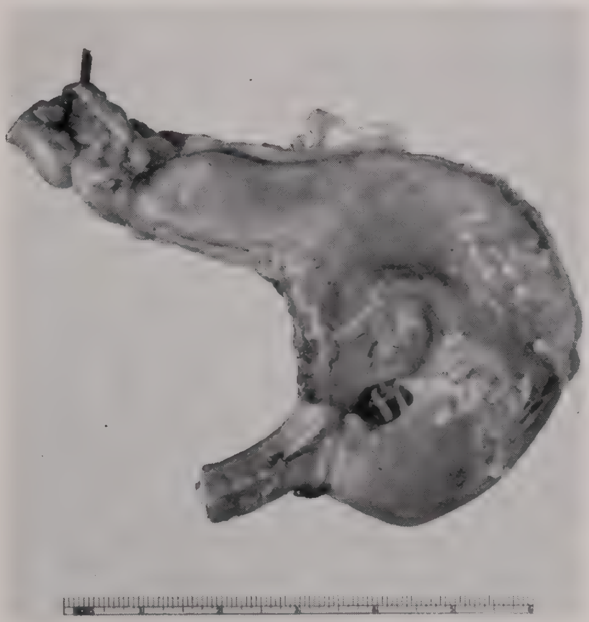

Fig. 2 — Dog study. This gastric rupture is located on the posterior wall near the esophagogastric junction.

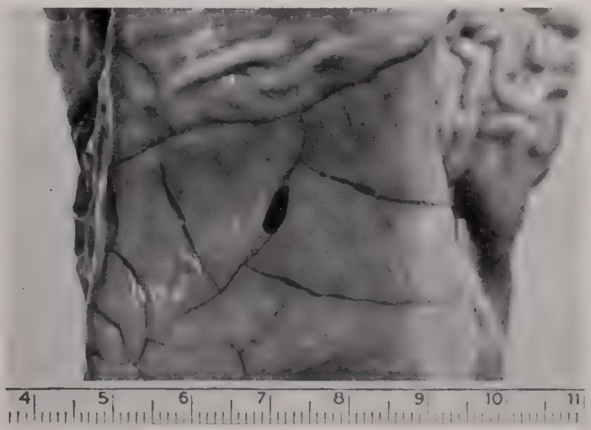

Fig. 3 — Dog study. Disruption is viewed from within the opened stomach. Note "cracks" in the mucosa. The submucosa split along one of the mucosal lines of injury.

External pressure applied to the abdomen caused rupture of partially inflated stomachs. No differences in bursting pressures or other rupture characteristics could be determined for normal anesthetized, anoxic, or recently sacrificed animals. Also, ruptures were similar in the air and the water-distended stomachs. The anterior wall was ruptured in a slightly larger number of cases than the posterior wall. Only 22 disruptions occurred at or near the lesser curvature, while most were found at or near the greater curvature. Some occurred near the esophagogastric junction (Figure 2), but the antrum never ruptured. Disruptions in all groups were similar in appearance. Only four dogs had small (1-2 mm.) perforations, while the remainder had large rents up to 6 cm. in length. The seromuscular coat splits first, followed by tears in the mucosa and finally in the submucosa (Figure 3). The submucosa is the strongest stratum of the stomach wall and the last to tear.

Perforation characteristics following air or water distention strongly resemble the "spontaneous" gastric rupture of the human newborn. The tears in the dog-stomach were similar in appearance to those seen in the infant and were located in the body of the stomach where the diameter is greatest. This is consistent with known stress variability in cylindrical objects. The greatest stress is present in that position of a tubular structure which has the greatest diameter. This may be expressed as:

$T = piDP$ T is the tension, while D is the diameter in centimeters and P is the intraluminal pressure in centimeters of water.

This is the same relationship pointed out by Wangensteen[11] in his study of perforation of the cecum in adults.

Conclusions

Diagnosis of a perforated viscus in the newborn should be suspected clinically and confirmed by x-ray film of the abdomen. Most visceral disruptions during this period occur in the stomach, and preoperative localization of the defect can be made with a fair degree of assurance. Our case demonstrates that even the huge ruptures can be adequately treated and the three-year follow-up shows no untoward growth and development.

Our experimental studies suggest that a fetal stomach, partly filled with fluid (swallowed aminotic fluid) and subjected to the rigors of the birth canal during a difficult delivery, may develop an intraluminal pressure sufficiently great to cause a gastric-wall defect. This defect could lead to complete disruption within a few days as the infant swallows liquid and air to further distend the stomach. The infant's air-swallowing characteristics and the need to eructate are well known.

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Life is ten per cent what you make it, and ninety per cent how you take it.

Erosion of the Splenic Artery from Gastric Ulceration

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GASTRIC ULCERS occur less frequently than their duodenal counterpart, but their tendency to give rise to massive hemorrhage is greater.[10] The site of bleeding is generally granulation tissue or erosion of intramural vessels, although involvement of major vessels, particularly one of the gastric arteries, is well known.[1,3,4,9]

We have recently observed three cases of catastrophic upper gastrointestinal bleeding resulting from ulceration of the splenic artery. In one the ulcer was benign, in the other two, malignant. All lesions were unusually large, located high on the posterior wall, and extending deeply into the pancreas. Review of the recent literature provided seventeen instances of hemorrhage from rupture of a splenic aneurysm into the stomach.[5,8,12] Involvement of a nonaneurysmal splenic artery by gastric ulcer erosion is mentioned only once.[6] The purpose of this report is to point out that large, chronic gastric ulcers may give rise to exsanguinating arterial hemorrhage, which must be treated by immediate surgery if the patient is to survive.

Case Reports

Case 1.

This 43-year-old white woman entered the hospital complaining of intermittent hematemesis for the two days preceding admission. There was a past history of bleeding after alcoholic excess. The hemoglobin concentration was 8.8 grams%, and the blood pressure, 80/50 mmHg. She was pallid and sweating. One thousand ml. of whole blood was given and

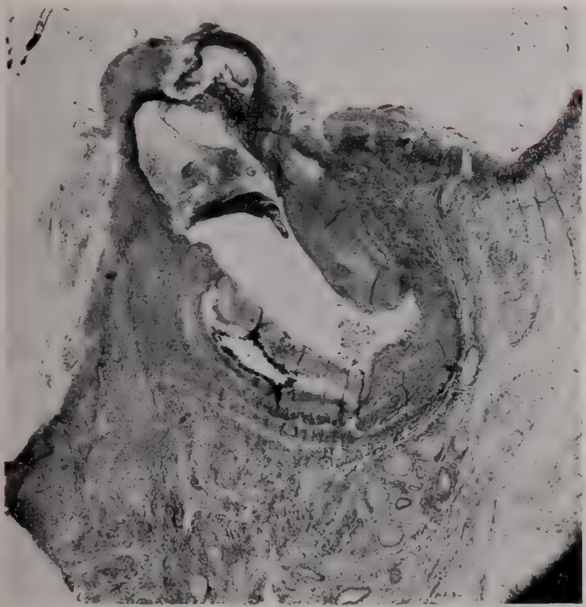

Fig. 3 — Stomach, Case 3. Splenic artery with necrosis of wall. Hematoxylin and eosin 10 X.

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nasogastric lavage performed until return was clear. She was then begun on a milk-drip regimen and carefully watched for evidence of renewed bleeding. Her condition remained stable for 48 hours, at which time she began to bleed massively, went into profound shock, and appeared moribund.

Immediate laparotomy was performed. The stomach was emptied of clots by gastrotomy, and the bleeding site was identified in a huge gastric ulcer high on the posterior wall of the stomach. The bleeding was controlled by digital pressure while her blood volume was replaced and anesthesia induced. The bleeding vessel was initially thought to be the left gastric artery, and while an assistant controlled the bleeding point, the celiac axis was rapidly dissected out and the left gastric artery ligated at its origin. This failed to control the bleeding and further dissection showed the vessel involved to be the splenic artery, which was then ligatured proximally and distally with cessation of bleeding. Biopsies of the crater showed a benign ulcer. A 75% gastrectomy was performed with a Billroth 1 anastomosis, the patient receiving a total of 16 units of blood on the day of operation. Her convalescence was complicated by the development of both gastric and jejunal fistulae. After prolonged hospitalization, she was discharged and, at the time of this reporting nine months postoperatively, she has regained her weight and pursues full activity.

Case 2.

This 50-year-old white male entered the hospital because of weakness, melena, and burning epigastric pain of two to three months' duration, his symptoms having become worse on the two days preceding admission. When initially evaluated in the Emergency Room, his blood pressure was 80/60 mmHg., pulse rate 112 per minute, and his hemoglobin concentration 8.3 grams%. He was given three units of blood and his stomach showed a clear return after lavage with saline. He was then begun on a continuous milk drip and observed for signs of further bleeding by nasogastric lavage, monitoring of vital signs, character of the stool, and hematocrit. Over the course of the next nine days no further bleeding ensued, and two upper gastrointestinal tract barium studies were carried out and reported as normal. Two days after the second set of x-rays, the patient began to bleed actively and required emergency laparotomy. At surgery, a giant ulcer measuring 8 x 10 cm. was found high on the posterior wall of the stomach with an arterial bleeder at its base. Dissection in the area showed that the splenic artery was the source of bleeding. This vessel was ligated; biopsies of the ulcer were taken; the ulcer was oversewn, and a vagotomy and pyloroplasty were performed. Frozen section diagnosis of the biopsies was benign, but permanent sections showed malignant foci. This patient also received 16 units of blood on the day of surgery. He has since been readmitted and re-explored. Widespread metastases at the time of the second operation precluded further resection.

Case 3.

This 60-year-old white male was admitted to Sinai Hospital, Detroit, in February 1965 because of epigastric pain, weight loss, intermittent nausea, and vomiting. During his evaluation, a large gastric ulcer was found on upper gastrointestinal series, and the patient underwent laparotomy. A malignant ulcer high on the lesser curvature was found, with metastases in the retroperitoneal space. Due to the extent of the lesion, it was not resected. He was well until March 1965, when he was admitted because of hematuria, and subsequently developed epigastric symptoms. Hematemesis first occurred four days prior to his demise and was mild in degree. His terminal event was a sudden, massive hematemesis.

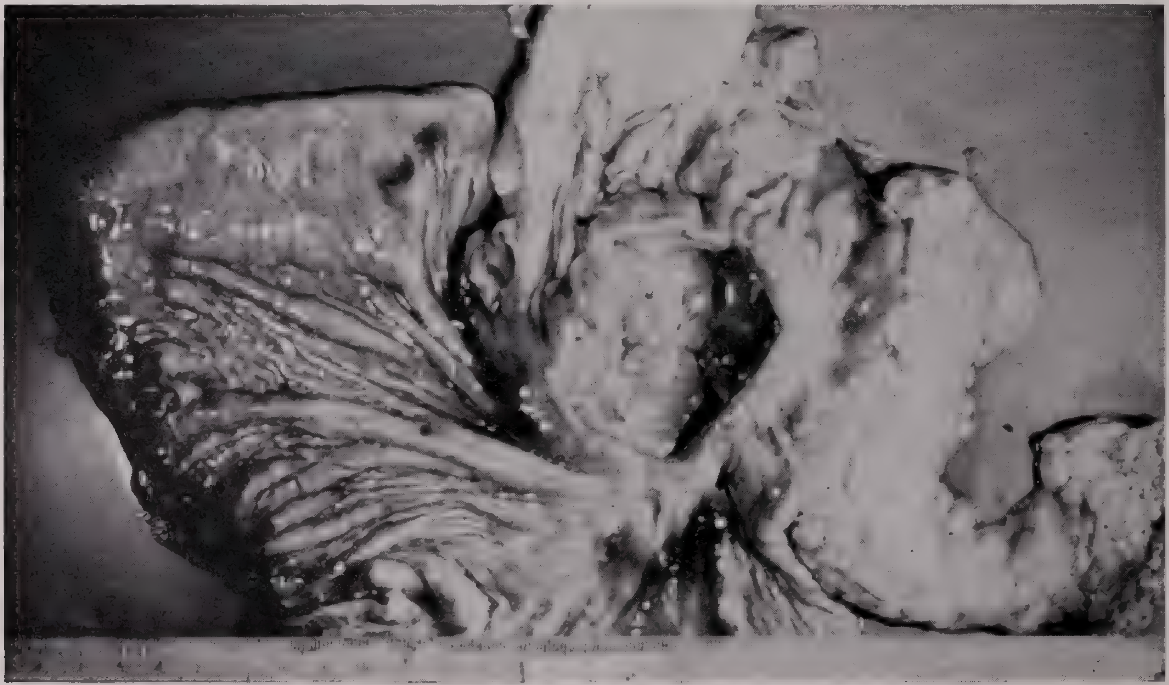

Fig. 1 — Stomach, Case 3. Large ulcer crater near esophageal junction. Pancreas is seen at right.

At autopsy, a large malignant ulcer high on the lesser curvature was found, with penetration into the pancreas and erosion of the splenic artery. Hematuria was due to a clear cell carcinoma of the left kidney.

Discussion

In most instances, gastrointestinal bleeding from peptic ulceration can be managed without immediate surgery.[1,7,10,11] In a few cases, due to the hazard of exsanguination, emergency operation is mandatory. When bleeding of such magnitude occurs. large vessels are likely to be involved. The arteries most often eroded are the gastroduodenal and left gastric.[10]

The rarity of reports of splenic artery erosion by either benign gastric ulcers or gastric carcinomas may be related to several factors. In surgery of massive upper gastrointestinal hemorrhage, the bleeding must be rapidly controlled if the patient is to survive. In Cases 1 and 2, each patient received 16 units of blood at surgery. Thus the urgency of hemostasis may outweigh the desire for delineation of the source of bleeding. Some cases of fatal hemorrhage from splenic artery erosion are not documented, because immediate surgery was not undertaken and postmortem autolysis obscured the bleeding point at autopsy. Since these same factors apply also to other name vessels which have been reported as the site of hemorrhage, other features unique to the splenic artery must be operative. The majority of gastric lesions, both benign and malignant, occur in the distal half of the stomach and thus are separated by some distance from the splenic artery. The course of this vessel, being superoposterior as well as lateral, further enlarges the distance between it and the posterior stomach wall. Thus, if an ulcer is to involve this artery, it must penetrate deeply into the pancreas.

Hemostasis may often be very difficult in these cases. Obviously, massive volume replacement is required and immediate operation necessary. The responsible vessel may not always be apparent and the best management of the problem not obvious. We have used both ligature of the vessel proximal and distal to the ulcer, and oversewing the vessel in the ulcer crater; we have found the former method preferable. While an assistant achieves control by digital pressure in the crater, dissection of the celiac axis and ligature of the splenic artery is carried out. The bleeding controlled, volume replacement and further operative procedures may then be

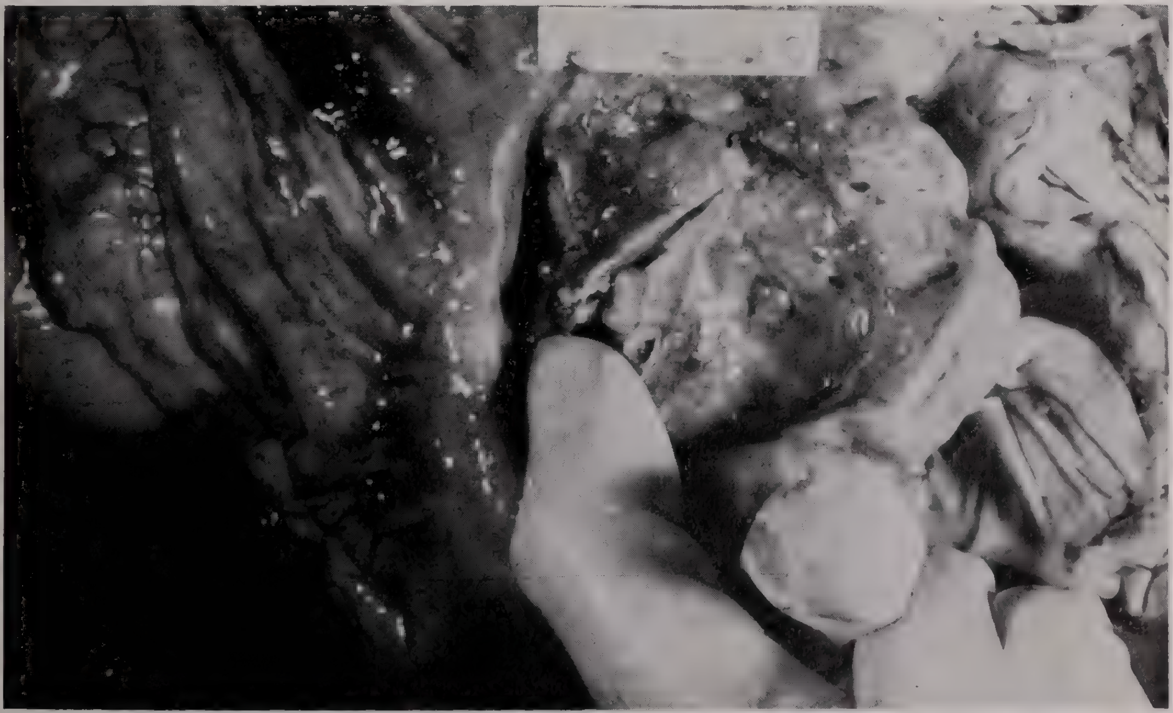

Fig. 2 — Stomach, Case 3. Splenic artery demonstrated in base of ulcer.

undertaken. With either method, development of pancreatic fistula is a possibility in the postoperative period. We have been impressed with the extraordinary size of these ulcers; all three measured 8 cm. in diameter. This, together with involvement of large portions of pancreas, suggests chronicity, although the history in all cases was brief. It has been said that lesions in the upper stomach give rise to fewer and less severe symptoms than those nearer the pylorus;[9] certainly the capacious fundus could hardly be the source of obstructive symptoms. These factors may explain the huge size of the ulcer and apparent procrastination of the patient in seeking treatment. In each of these cases a preliminary, less severe bleeding episode preceded the massive one. Such "sentinel bleeds" have been described when large vessels are the site of hemorrhage.[2]

Radiologic examination is rarely helpful in these individuals; the diagnosis is made at laparotomy. In Case 2, upper gastrointestinal series on two separate occasions were read both initially and retrospectively as normal, despite the presence of a huge ulcer. Perhaps the size of the ulcer or presence of clot within its crater precludes recognition. The poor condition of the patient with truly massive bleeding certainly prohibits detailed preoperative evaluation.

The differentiation of malignant from benign lesions under circumstances imposed by emergency surgery is difficult. Frequently, frozen sections are not available during the night and final diagnosis of stomach tissue may require permanent sections. Most large, deeply penetrating ulcers grossly appear malignant, regardless of their true nature. In the absence of metastases, some ulcers must be treated as benign, the immediate bleeding situation remedied and definitive surgery deferred until a final diagnosis is made. This is particularly true when the patient is moribund, when massive transfusions have been given, and when limitation of further anesthesia is desirable.

Summary

Of the three cases of massive upper gastrointestinal hemorrhage from ulceration of the splenic artery malignancy accounted for two. The features which suggest splenic artery involvement are a huge ulcer, high on the posterior stomach wall, with deep penetration into the pancreas. Chronicity is certainly suggested by these factors, although the history was brief in all three cases. Premonitory "sentinel bleeding" before the massive, frequently fatal, hemorrhage is common, and an aggressive surgical approach is required.

We wish to thank Drs. Eugene Copuzzi and Molly Lo of Sinai Hospital, Detroit, for permission to use Case 3 and for providing material helpful in this presentation.

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Alarming

America is not immortal and there are today signs in American life of an alarming deterioration in the things of the spirit. — Francis Cardinal Spellman

The Doctor and Literature

Literature is thought in words committed to permanent form by writing. Unlike other art forms like painting or acting, it never decays and never deteriorates.

The lot of the creative writer, like Gilbert's policeman in the *The Pirates of Penzance*, is not a happy one. The author is bedevilled by his God-given talent which never allows him to be at peace with himself. His mind seethes with ideas clamoring to be set down in writing.

> "The poet's eye in fine frenzy rolling
> Doth glance from heaven to earth, from
> earth to heaven
> And as imagination bodies forth
> The form of things unknown
> The poet's pen turns them to shapes
> And gives to airy nothing a local
> habitation and a name."

Because he lives in the world of his own imagination the writer is usually at odds with the age in which he was born into a world he never made. Many authors like St. Paul are born out of due time.

Creative geniuses are frequently feared and hated by their contemporaries, who persecute them during their lifetime and praise them extravagantly after death. The creative writer has a vast and warranted egotism which often makes him rude and inconsiderate of the feelings of others. He is usually impossible to live with. Shakespeare and Dickens both deserted their wives for younger women. Milton called his wife a "mute and spiritless mate, a bit of earth and phlegm.' And the long suffering Mrs. Carlyle, after a lifetime with Thomas, said that a genius was "gang ill to live with."

A writer like Sinclair Lewis may enjoy sudden prosperity and success early in his career and never be able to duplicate his triumph. Too often sudden fame and fortune are followed by a dismal anticlimax of years of neglect and oblivion. The author often dies unwept, unhonored and unsung.

Every writer, from Milton, who mourned "How soon hath time the subtle thief of youth stolen on his wing my three and twentieth year" — to John Keats who had fears that "I will cease to be before my pen has gleaned my teeming brain," lives in the constant fear of dying before he has put on paper the immortal work he has it in him to write.

Authors, being nonconformists, are usually "agin" the government. England has always been harsh in her treatment of her greatest authors. Behind many a famous writer was a doctor who not only gave him professional care, but what was much more important . . . kindness and understanding when the author was in the agonies of creative composition or beset by the slings and arrows of outrageous fortune, shot by dull finished clods, untroubled by a spark.

William Makepeace Thackeray dedicated his novel to his friend and physician, Dr. Henry Thompson, whom he credited with saving his life.

When Samuel Taylor Coleridge exhausted his poetic gift by writing in ten months *The Rime of the Ancient Mariner* and *Christabel*, 1797-1798, he resorted to opium to alleviate the pains of frustration. Unable to control his addiction after ten years of degradation, he sought refuge with James

Continued on page 110.

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In *men:* in whom trichomonads have been demonstrated, one 250-mg. oral tablet b.i.d. for ten days.

Contraindications

Pregnancy; disease of the central nervous system; evidence or history of blood dyscrasia.

Precautions and Side Effects

Complete blood cell counts should be made before and after therapy, especially if a second course is necessary.

Infrequent and minor side effects include: nausea, unpleasant taste, furry tongue, headache, darkened urine, diarrhea, dizziness, dryness of mouth or vagina, skin rash, dysuria, depression, insomnia, edema. Elimination of trichomonads may aggravate moniliasis.

Dosage Forms

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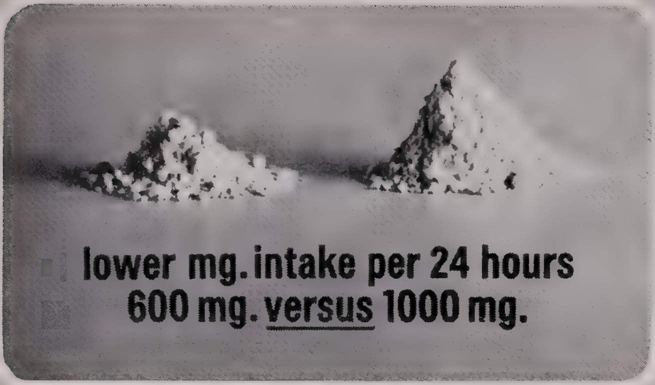
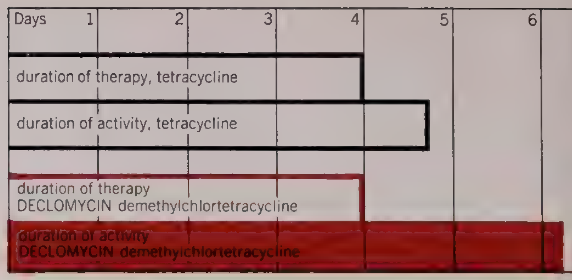
Research in the Service of Medicine



lower mg. intake per 24 hours
600 mg. versus 1000 mg.



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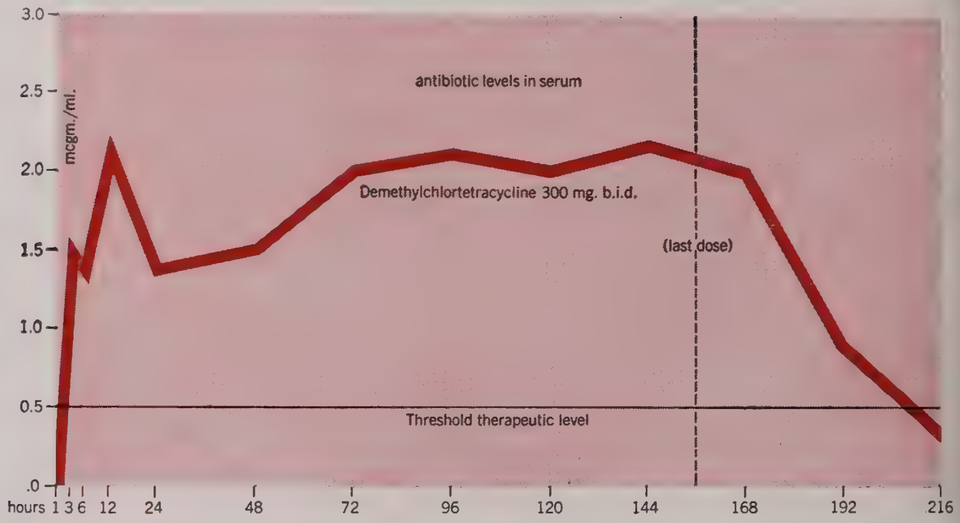

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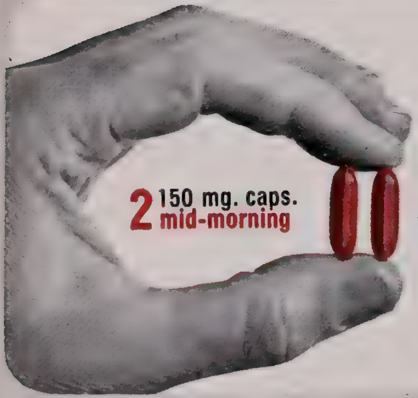

12 hours
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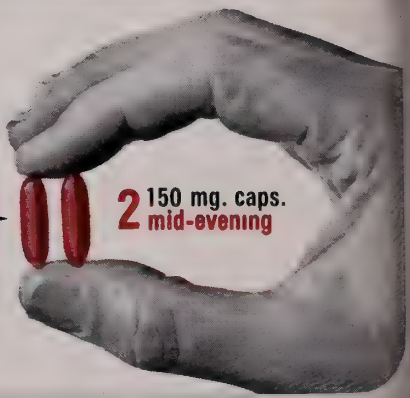

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Editorials

Influences of the University of Minnesota Upon the Wayne State University School of Medicine

Perhaps the most perilous and at the same time the most frequently undertaken literary assignment is to assess the influence of one person upon another. The peril is doubled when one tries to measure the effect of one institution upon another.

It would appear that the genetic lines of influence should be easy to follow in two universities and that in any two medical schools the task would be even more simple. However, medical schools are as complicated as the universities which nurture them. It would be logical that medical schools have much in common and that their objectives would be alike. Inasmuch as each does grant a degree, which after certain technicalities and a great deal of effort entitles the holder to practice his science and art, medical schools are very similar. The curricula are surprisingly alike but astoundingly dissimilar in their implementation. However, each seems to be a blend of strict scientific and scholastic discipline with a wide variety of human experience which has not been arranged in any very orderly way. It is this experience which permits the full flowering of human wisdom and the parallel development of convictions based upon empiricism.

The one unusual characteristic in the relationship of these two medical schools, Minnesota and Wayne State, is the relatively large number of faculty which have been drawn to the one from the other. The main flow has been from west to east. It is interesting that most of this faculty movement has taken place within the last thirty years.

Raymond B. Allen

It began with the appointment of Raymond B. Allen as Dean of Wayne State University School of Medicine in 1936. Dr. Allen was graduated from the University of Minnesota School of Medicine in 1928. During his three short years he brought to Detroit twelve faculty members, a number of whom were to influence the course of the Wayne State University School of Medicine. As might be expected, some of this group felt their institutional responsibilities keenly; others, to paraphrase Jacob Henle, looked upon the School as a "cow to be milked." Indeed, they behaved as any dozen men drawn at random from any population.

The influence of Raymond Allen and his energetic and skillful leadership mark a definite turning point in the affairs of the Wayne State University School of Medicine. He began the development of the full-time system in both preclinical and clinical departments. The importance of Allen's influence is difficult to overestimate. Firm and

Continued

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unwavering was his insistence that the faculty standards of Wayne be raised and that teaching in a medical school was an activity deserving the full attention of any faculty member. This was accomplished in an ambient medical opinion hostile to the development of a strong medical school. It was no mean feat.

His administrative abilities were quickly recognized by the University of Illinois. Before 1939 had ended, he was lured to Chicago to become Executive Dean of the Chicago Colleges of the University of Illinois. This was followed by his call to the presidency of the University of Washington, the Chancellorship of the University of California at Los Angeles, and to extremely sensitive and vital Federal Government posts.

In the years after Raymond B. Allen's deanship, his firm stands and sound administrative policies were challenged many times, but the directions of development were not reversed. Allen brought Edgar Norris (M.D., Minnesota, 1919) to Wayne State University in 1938, not realizing that he was to follow him in the decanal chair less than two years later. Norris presided over the affairs of the Medical School until February of 1945. From the beginning, his task was difficult. A part of this difficulty was the tremendous burden imposed by the times. The lack of proper facilities was an additional factor. Bruised egos and abraded sensibilities also made their contributions. These human qualities come to full flower in faculties, as in other groups, under the stress of overwork and wartime necessities.

Edgar Norris

In these war years, Edgar Norris was bold enough to undertake the planning of a medical center. The planning of such a group of medical activities was original and, on paper, not unlike a number of university medical centers now in existence. The plan stirred the interest of a number of influential Detroit citizens and in other times would have succeeded. It is sad, indeed, that it could not have been started with Dr. Norris to guide it. The importance of the adventure was that the medical center idea was put into the minds of Detroiters and is now in the stage of implementation. There have been many modifications; but the idea of gathering in one place the disciplines of medicine and of the paramedical sciences has now become an accepted way of undertaking the tremendously complicated and costly task of educating people in the health sciences.

Lawrence Berman and Gordon H. Scott

The influence on Wayne State's School of Medicine exerted by Edgar Norris did not end with his planning of a medical center. He brought twenty-two faculty members from Minnesota to Wayne in the five years he served as Dean. Among them is Lawrence Berman (M.D., 1937) who later served as Chairman of the Department of Pathology for three years and did much to further research programs in the School of Medicine. Just before Dr. Norris resigned as Dean, he offered the post of Chairman of Anatomy to the writer, who later served as acting Dean from 1948-50 and as Dean from 1950-63, and is now Vice President in Charge of Medical School Development.

It might be expected that Dr. Norris, being a pathologist, would have brought more pathologists from Minnesota than from other disciplines. This was not the case. During his five-year term, graduates of Minnesota were called to posts in internal medicide, pediatrics, surgery and several of its specialties. The effect was to strengthen, insofar as wartime permitted, the entire fabric of the School of Medicine at Wayne. Of the twenty-two Minnesota graduates brought by Dr. Norris, two became heads of important departments, Lawrence Berman in Pathology and Gordon H. Scott in Anatomy. Of the Minnesotans brought by Raymond Allen, two became heads of important departments, Edgar Norris in Pathology and James Lofstrom (M.D., 1932) in Radiology. Dr. Lofstrom served the school of Medicine for nearly 30 years and organized an effective department for teaching, research and service. Under his direction the first cobalt therapy equipment in the State was installed. He also was in charge of the linear accelerator installation — the first in Michigan.

Continued

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Allan Thal and Raymond Read

Another department head from Minnesota was appointed in 1961. Dr. Alan Thal did not take his medical degree from Minnesota but served as a faculty member, as did his colleague, Raymond Read. Dr. Thal is now chairman of the Department of Surgery and Read an Associate Professor of Surgery. They are at present developing an extensive program in open-heart surgery, distinctly reminiscent of some of the activities in Minneapolis, and in the fundamental aspects of shock.

Most of the faculty brought from Minnesota were full-time. A goodly number have stayed and are today holding appointments; others have left to assume faculty or research opportunities elsewhere, and some have gone into private practice. During the years since 1936, the University of Minnesota has sent more faculty people to Wayne State than any other one institution outside the State of Michigan. There is no doubt that the University of Minnesota has produced faculty members who have profoundly influenced the ultimate course of our Medical School. This is because a Minnesota graduate knows what a good University and a good medical school should be; it can also be credited to the experience and knowledge he brings to bear on his discipline: surely as good a base from which to develop a strong faculty as could be devised.

Gordon H. Scott, Ph.D.*
Detroit, Michigan

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*Vice President for Medical School Development, Wayne State University.

Wayne State University and the Detroit Medical Center

THE NEEDS of the State of Michigan for more physicians have been ably documented and presented by several advisory groups whose studies have led to the recommendation that the School of Medicine at Wayne State University be expanded. This led to the decision to increase the entering class of medical students at Wayne from 125 to 200, and, perhaps ultimately, to 250. This increase will add the equivalent of another medical school in Michigan.

More than 10 years ago, a group of private citizens determined that Detroit must solve the grave problems confronting the major downtown hospitals because of the increasing spread of slums. The concept of a new Medical Center was developed, and the University with its medical school became a key part of the development. The School of Medicine at Wayne is unique in that it is the only medical school in a metropolitan area of about 4 million. The faculty is heavily involved in community service and community problems. These responsibilities are burdensome, but, as the Medical Center develops, they also represent a magnificent opportunity to relate medical education to the changing patterns of medical care.

The hard work, planning, and cooperative efforts of the past decade now find nearly 250 acres being cleared by the City of Detroit in downtown Detroit through urban renewal. This area is the site of the Detroit Medical Center, which is a complex of resources for teaching, research, patient care, and community service. This complex involves Wayne State University, the City of Detroit with its Detroit Receiving Hospital, the Federal government with a proposed new Veterans Administration Hospital, and private hospitals: namely, Harper, Grace, Children's, Woman's, and the Rehabilitation Institute. These private hospitals are planning extensive new construction, as well as renovation. A Medical Center organization is being developed between the University and these hospitals for the purpose of defining common goals relating to the teaching and research already being carried out in these private institutions.

Continued

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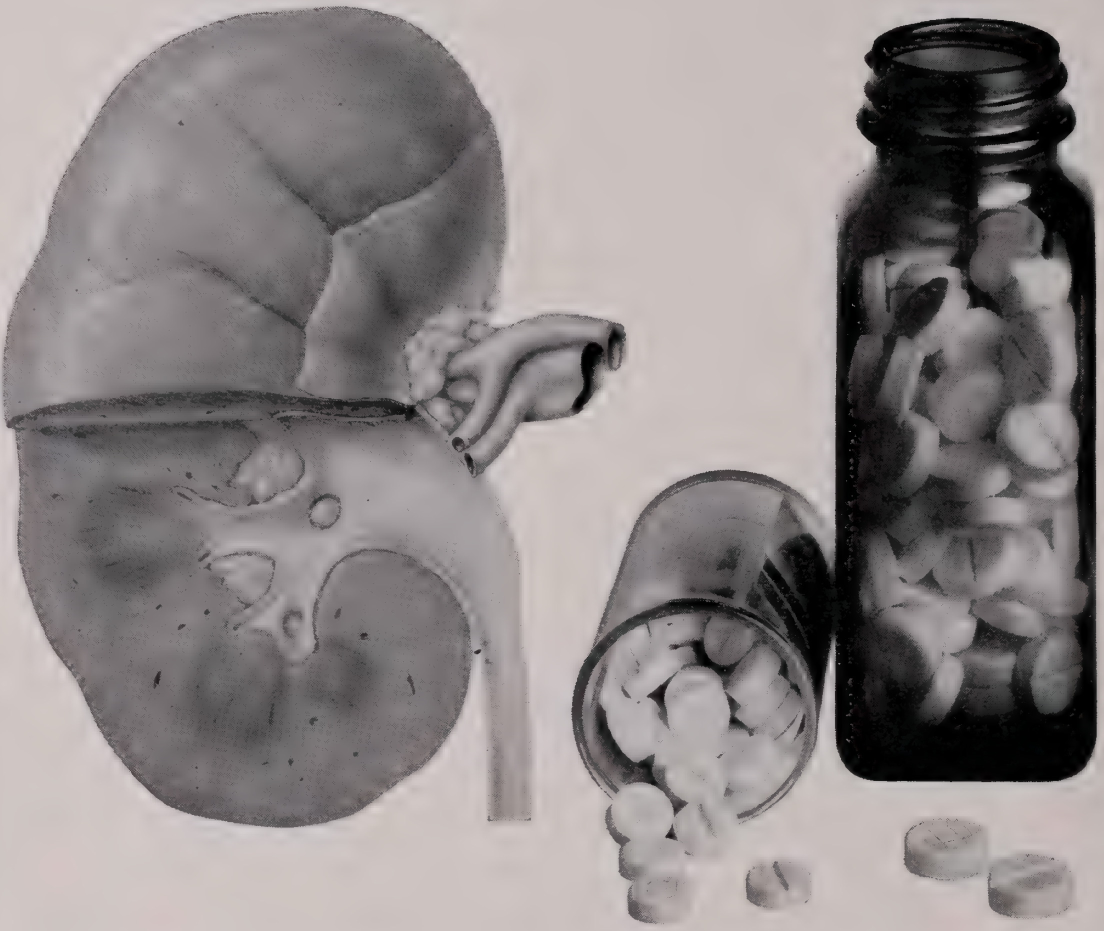

understanding... precedes development

The development of chlorothiazide and probenecid were events of major importance, but perhaps even more important for the future was the Renal Research Program by which they were developed. When Merck Sharp & Dohme organized this program in 1943, it was expressing in action some of its basic beliefs about research:

- Many problems connected with renal structure and function were still undefined or unsolved. The Renal Research Program would begin its basic research in some of these problem areas.
- From knowledge thus acquired might come clues to the development of new therapeutic agents of significant value to the physician.

For example, the Renal Research Program put fifteen years into this search before chlorothiazide became available. But because these years had first led to a greater understanding of basic problems, the desired criteria for chlorothiazide existed before the drug was developed.

Along with other research teams at Merck Sharp & Dohme, the Renal Research Program continues to add new understanding of basic problems—understanding which will lead to important new therapeutic agents.

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where today's theory is tomorrow's therapy

The University will have new research and instructional buildings in the Center which will enable it to accept more medical students. The first building, a 4-million-dollar research facility, has just been finished and is almost completely occupied. The teaching to be carried out in the Medical Center will include many different kinds of students. It cannot be emphasized often enough that modern, comprehensive health care involves much more than the physician, and that educational institutions concerned with health teach many more kinds of students than medical students.

We are engaged in an intensive study of our curriculum, because we realize that we have an extraordinary but short-lived opportunity, as the Center develops, to make those changes in medical education that are demanded by the changing pattern of medical care. Now in the years to come we will be dealing with a population which will be increasing dramatically. The increase is especially noticeable in the young and old groups. Furthermore, these people are concentrated in urban areas, and probably 20% make a major change of residence each year. Today, the major causes of death are due, not to infectious agents, but rather to cardiovascular disorders, neoplasms, and trauma. Because of these major changes, we must, by every means at our disposal, seek to instil in our medical students the idea of looking at each patient in terms of his family, environment, culture, and background or heredity, together with the natural history of the disease that he may have. We must make the student see that the acutely ill patient admitted to the hospital with an inflamed liver, for instance, is not just a "case" to be perfunctorily treated for his liver ailment alone and then arbitrarily released after a series of normal liver-function tests. The student must realize the importance of family, community, and socioeconomic factors in relation to health, and that treatment of symptomatic disease is but a part of the total picture of health care, which includes comprehensiveness and continuity.

A University by tradition is concerned with past, present, and future, and in keeping with this tradition a medical school must prepare students for tomorrow's medicine as well as for today's. I believe that the proper discharge of these traditional responsibilities by our faculty will ensure the success of the Medical Center. The University of Minnesota has a stake in this center because a significant number of our faculty have been drawn from the University of Minnesota. These men, who come from a medical school known for its high academic standard and strong University orientation, have been and continue to be a major influence on the developments at Wayne State University.

Ernest Gardner, M.D.
Detroit, Michigan

Detroit Receiving Hospital*

Its Relationship to the University of Minnesota Medical School and Medicine in Minnesota

DURING THE past 42 years many young graduates of the University of Minnesota Medical School have come to Detroit Receiving Hospital to intern. Some have come or have remained to serve residencies, and a few, already trained at Minnesota, have joined the staff of Detroit Receiving Hospital as members of the faculty of Wayne State University School of Medicine.

Dr. Raymond Read, who was graduated from the University of Minnesota Medical School and received his surgical training there, suggested that a description of this flux of young physicians from the University of Minnesota Medical School to Detroit Receiving Hospital be incorporated in this issue of "MINNESOTA MEDICINE."

Since 1923, one hundred and twenty-nine graduates of the University of Minnesota

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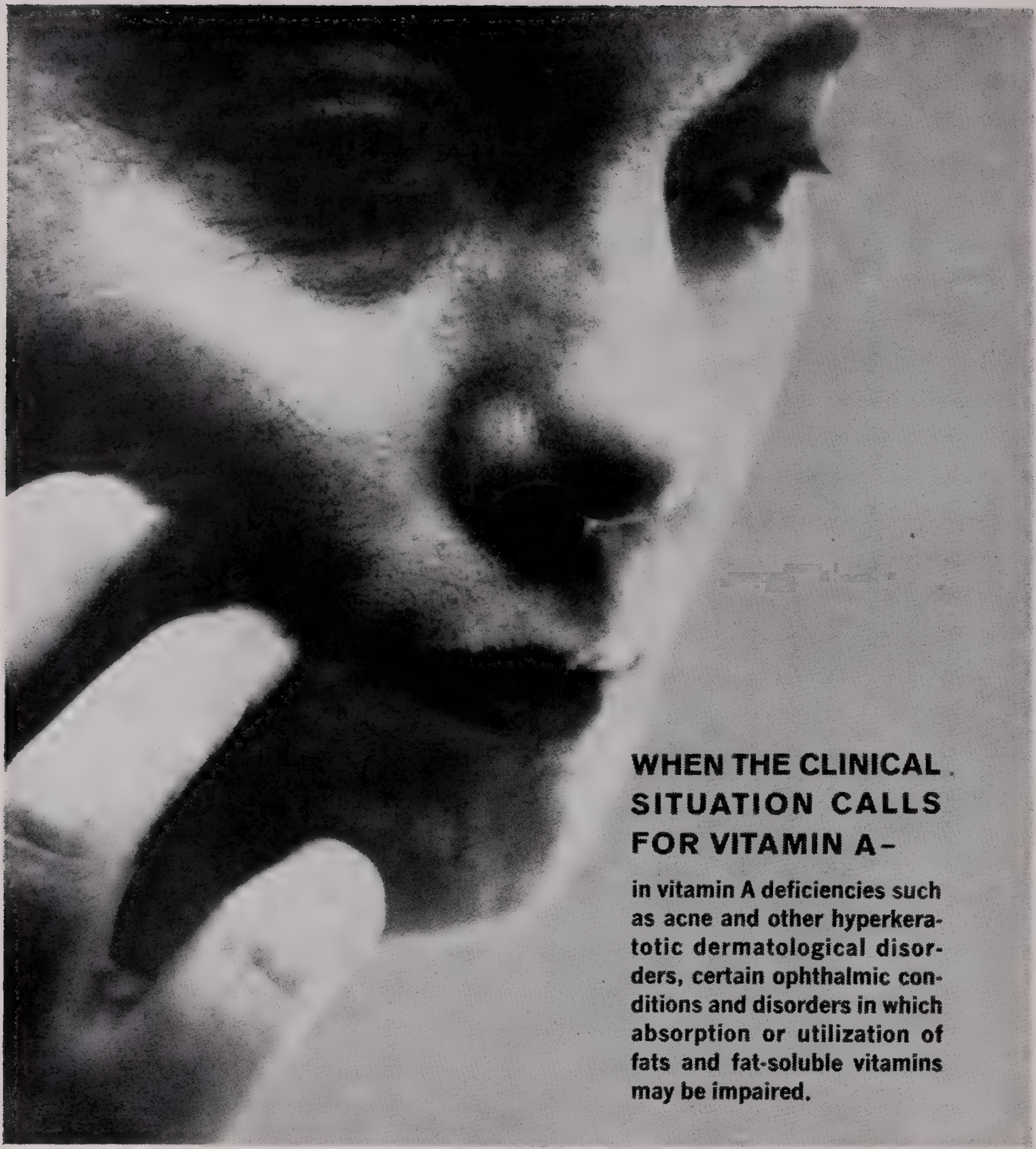
*Presently called the Detroit General Hospital.



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Medical School have interned at Receiving Hospital. As might be suspected and as will be seen shortly, these numbers are too large to have been fortuitous.

Detroit Receiving Hospital, a municipal institution under the administration of the Welfare Department of the City of Detroit, was opened October 12, 1915, "to care for the sick poor of the City and others." New wings were added in 1921 and 1927 and on January 5, 1950, its administration was transferred from the Welfare Department to the Detroit Board of Health. In 1952 the eight-story air-conditioned Farwell Wing was completed and occupied.

There is neither need nor space for a review of the history of the University of Minnesota Medical School here, but it should be pointed out that from 1918 to 1952 the University of Minnesota granted the Bachelor of Medicine (M.B.) degree on graduation and the Doctor of Medicine (M.D.) degree following completion of the required internship. In 1953 this was changed back to the original system in operation prior to 1918, in which the M.D. degree was awarded upon graduation.

Jennings C. Litzenberg, Professor and Head of the Department of Obstetrics and Gynecology at the University of Minnesota from 1914-38 and Chairman of the Intern Committee for most of the period, was responsible for the link between the University of Minnesota Medical School and Receiving Hospital. When an internship became a requirement for the M.D. degree at the University of Minnesota, the Intern Committee then proceeded to classify hospitals according to their assessment of these hospitals' educational value for interns. Dr. Litzenberg visited many hospitals and sent out many questionnaires. Supplemental information was obtained from confidential sources. During this period hospital superintendents or chiefs of staff were required to report in detail twice yearly upon the performance of Minnesota interns; and in turn the interns were required to report similarly as to the quality of teaching they received, the responsibility given them, the quality of patient care and the standards of performance demanded of them. The reports of these graduates on the hospitals in which they interned were available to Minnesota seniors in the office of the Intern Committee. During this period the Intern Committee actually supplied internships for those graduating from the University of Minnesota Medical School. The Intern Committee agreed to supply a given number of interns to a given hospital, and that hospital in turn agreed to reserve this number of internships for the Minnesota graduates named by the Committee.

Each senior would list his choices in order of his preference from the list of approved hospitals, and whether or not he obtained his first choice depended upon his class standing. For many years three to five graduates ranking near the top of their class at Minnesota came to Receiving Hospital to intern. This system changed after the war and now has been replaced by the National Intern Matching Plan.

Of the 141 graduates of the University of Minnesota Medical School who came to Detroit Receiving Hospital in one capacity or another (129 as interns), five are deceased; two are retired and nine others are not shown in the 1963 Directory of the American Medical Association. Fifty returned to Minnesota to practice, twenty-two remained in Michigan and fifty-one were practicing in other states in 1963. The achievements of these physicians have been outstanding. In 1963, 73 were certified specialists, and 18 were specialists without certification. Forty-two were members of medical school faculties. Thirty of these were voluntary faculty members. Twelve were or had been full-time faculty members. Five of these were full professors (two were departmental chairmen and two had been chairmen of departments). On the present staff of Receiving Hospital there are five of professorial rank: Dr. James Lofstrom, Professor of Radiology, Dr. Alan Thal, Professor and Chairman of Surgery, Dr. Lawrence Berman, Professor of Pathology, Dr. Raymond Read and Dr. Ernest Berkas, Associate Professors of Surgery.

Dr. Wendell Hall, after interning at Detroit Receiving Hospital, returned to Minneapolis

Continued

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Side effects: Drowsiness may occur and, rarely, ataxia, usually controlled by decreasing the dose. Allergic or idiosyncratic reactions are rare, generally developing after one to four doses. Mild reactions are characterized by an urticarial or erythematous, maculopapular rash. Acute nonthrombocytopenic purpura with peripheral edema and fever, transient leukopenia, and a single case of fatal bullous dermatitis after administration of meprobamate and prednisolone have been reported. More severe and very rare cases of hypersensitivity may produce fever, chills, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, anaphylaxis, stomatitis and proctitis. Treatment should be symptomatic in such cases, and the drug should not be reinstituted. Isolated cases of agranulocytosis, thrombocytopenic purpura, and a single fatal instance of aplastic anemia have been reported, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity has been reported, usually after excessive meprobamate dosage. Suicidal attempts may produce lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

Usual adult dosage: One or two 400 mg. tablets three times daily. Doses above 2400 mg. daily are not recommended.

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to continue his training in internal medicine and is currently Professor of Medicine and Head of the Medical Department at Minneapolis Veterans Hospital.

Two others have had distinguished military medical careers. Captain John S. Cowan, M.C. USN, an internist, is currently commandant of the Philadelphia Naval Hospital. Prior to this he was Director of Medical Affairs (Supreme Allied Commander NATO) and Fleet Medical Officer (U.S. Atlantic Fleet, Norfolk). Colonel Robert J. Kamish M.C. USA, a surgeon, was chief of Surgery at Gorgas General Hospital and had been Chief Surgical Consultant (Europe) 1956-58 and chief of Professional Services at Letterman General Hospital 1960-62.

If space permitted, many other distinguished careers could be recounted, for many other men have come to occupy positions of distinction in their specialties throughout the Midwest and the West. It is apparent that the relationship between these two institutions has been a fruitful one. While it has benefited medicine most in Minnesota and Michigan, its effect has been felt throughout the United States.

Muir Clapper, M.D.
Detroit, Michigan

I should like to express my thanks for the generous help given me by Mrs. Edith A. Lindberg, formerly Secretary to the late Jennings C. Litzenberg, M.D., by H. Mead Cavert, M.D., Associate Dean, The University of Minnesota Medical School and by Donald B. Frane, M.D., all of Minneapolis.

References

1. Litzenberg, J. C.: Administration of Internships. J Ass Amer Med Colleges 9:216, 1934.
2. Howard, Robert B.: A Directory of the Alumni of the University of Minnesota Medical School, November 1954.

Air Pollution and Health*

THE TUBE bridges a busy street in downtown Detroit. Five to ten thousand cubic feet per minute of street air is drawn through the tube and delivered into an adjacent laboratory. In that location a number of automatic systems constantly monitor the quality and quantity of eight different constituents. Animals exposed to the intake air are under study in order to assay their physiologic, anatomic and biochemical responses. The air we breathe, in relation to occupational and nonoccupational situations, may contain a variety of pollutants which have toxic effects; accordingly they have the capacity to induce disease in strategic segments of the respiratory tract and lung. In addition, certain inhaled pollutants are absorbed from the lung and thus may provoke a variety of functional and structural changes in nonpulmonary tissues and organs of the body, the nature and extent of the adverse effects depending upon a number of variable factors. From the physical viewpoint, the pollutant may occur in the form of dust, fume, mist, vapor or gas. Although much is still to be learned about pollutants, the air in most highly industrialized urban situations usually includes a large number of inorganic compounds having components which range from aluminum to zinc in the alphabetic list of elements. Among the common gaseous pollutants there may be excessive concentrations of carbon monoxide, nitrogen oxides, sulfur oxides, aldehydes, hydrocarbons, chlorides and fluorides. Oxidants also occur, and in the presence of sunlight they may react with other pollutants to form new compounds. Radioactive substances may comprise a considerable portion of a polluted atmosphere. Pertinent examples include gases and vapors created by chemical processes, gases and fumes in foundry situations, mists and vapors in spraying operations, dusts and fumes of mineral substances generated by uncontrolled mining, milling and processing operations, dusts of demolition

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*See cover photograph.

The tell-tale lesion on the back of her neck

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work, and last but not least the products entrained in vehicular exhausts and stack effluents.

The physical nature of the airborne pollutants, especially in regard to their mass (total weight), shape and size, determine in large measure whether or not the particulates remain suspended in the atmosphere and can then pass the defense barriers of the respiratory tract and gain entrance into the finer airways and alveoli of the lungs.

It is generally recognized that particle size has an inverse relationship to its ease of entrance into the bronchopulmonary system. The real issue, however, concerns the point of declining size at which the inverse relationship may cease to exist. Resolution of that issue is difficult pending more precise knowledge concerning the number of ultramicroscopic particles in the inhaled air and the kinetic properties of those particles, especially in relation to their penetration, primary deposition, retention and transport in the airways and lungs. Concentration of the pollutant in the inhaled air is an exceedingly important factor which operates to govern the amount that is brought into contact with the target tissue. The tolerable atmospheric concentration of many pollutants has been prescribed in terms of safe threshold values (MAC: maximum acceptable concentration) which should not be exceeded in occupational situations, if the adult and relatively healthy exposed employee, working approximately eight hours daily, is to remain free of occupational respiratory disease. Those values, however, must be cautiously applied to community air which involves a potentially continuous twenty-four-hour exposure of a population which includes the very young and the very old, the healthy and the sick, the resistant and the highly sensitive individual.

One of those variables which influence the nature and extent of the biologic damage to tissues, concerns the duration of the exposure, viz., whether it is brief or prolonged, continuous or intermittent. Within certain limits, brief or intermittent exposures to extreme amounts of a pollutant are capable of producing acute damage, which may either resolve or leave in its wake a series of subtle and gradually developing chronic effects. Similar effects may result from prolonged or continuous exposure to low atmospheric levels of certain pollutants. In regard to effects, it should be recognized that not all pollutants are intrinsically toxic. Some are relatively inert and nontoxic, whereas others, either alone or in combination, are biologically active and toxic. Not all persons react alike; some are partially or almost completely resistant, whereas others are unduly susceptible and respond early with subjective and objective deviations from the norm.

In final analysis, the toxic effects of inhaled atmospheric pollutants are determined by an interplay between the competing forces inherent in the pollutant per se and in the exposed person, especially the older individual who may have structural and functional impairment unrelated to his inhalation of an atmospheric pollutant.

Arthur J. Vorwald, Ph.D., M.D.*
Detroit, Michigan

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*Department of Occupational and Environmental Health, School of Medicine, Wayne State University.

Aneurysmal Abscess

MYCOTIC ANEURYSMS* occurring as secondary complications of septicemia have been recognized since their first description by Osler in 1885. Infection and destruction of an adjacent arterial wall by a necrotizing abscess likewise, has been appreciated for more than a century. However, Huebl and Read, in their paper, "Aneurysmal Abscess,"** describe two new etiological modalities, iatrogenic and egogenic.

Two of their cases, iatrogenic in origin,

Continued

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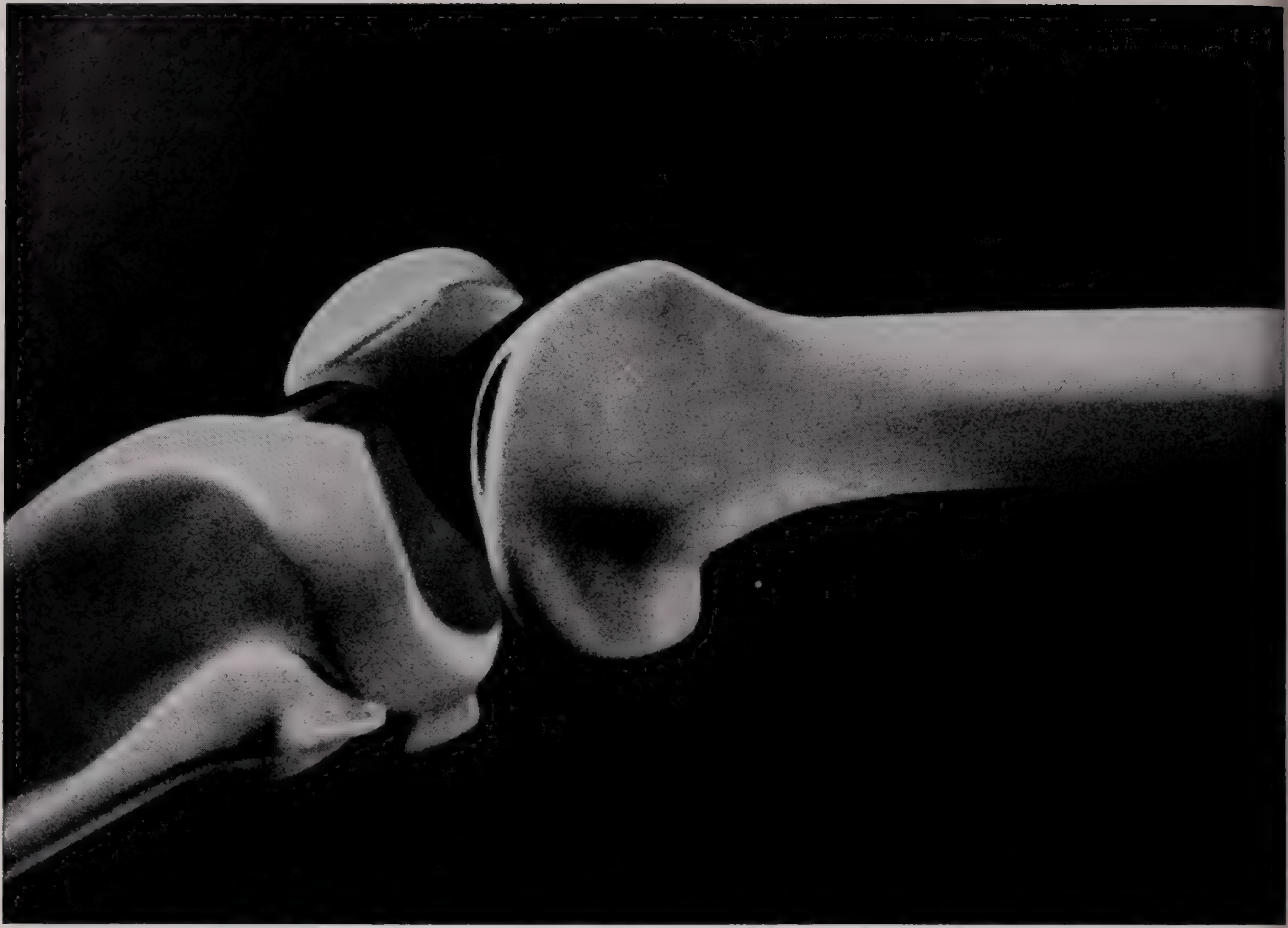
*See Test Your Word Score Page 97.
**See page 11.



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A large number of investigators have reported major improvement in about 75% of cases. Some patients have gone into remission. Relief of stiffness and pain may be followed quickly by improved function and resolution of other signs of inflammation. And Butazolidin alka is well tolerated, especially since it contains antacids and an antispasmodic to minimize gastric upset.

Contraindications
Edema, danger of cardiac decompensation; history or symptoms of peptic ulcer; renal, hepatic or cardiac damage; history of drug allergy; history of blood dyscrasia. The drug should not be given when the patient is senile, or when other potent drugs are given concurrently. Large doses are contraindicated in patients with glaucoma.

Precautions
Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patient should be closely supervised and should be warned to report immediately fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools. Make regular blood counts. Use greater care in the elderly.

Warning
If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy.

Adverse Reactions
The most common are nausea, edema and drug rash. Hemodilution may cause moderate fall in red cell count. The drug may reactivate a latent peptic ulcer. Infrequently, agranulocytosis, generalized allergic reaction, stomatitis, salivary gland enlargement, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported but cannot definitely be attributed to the drug. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hepatitis, jaundice, and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently.

Dosage
The initial daily dosage in adults is 300-600 mg. daily in divided doses. In most instances, 400 mg. daily is sufficient. When improvement occurs, dosage should be decreased to the minimum effective level: this should not exceed 400 mg. daily, and is often achieved with only 100-200 mg. daily.

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followed carotid angiography done by direct needle puncture of the carotid arteries. Both cases developed paravascular staphylococcal infected hematomas which destroyed the arterial wall. The other two cases, egogenic in origin, followed habitual intrafemoral vein self-injection of paregoric by addicts. Inevitable spillage of this necrotizing camphor compound into the paravascular tissues of the femoral artery produced abscesses which destroyed the arterial wall. Aneurysmal abscess resulted in all four cases.

These authors describe the bold surgical intervention required to drain these abscesses and to control the vascular disruption and the lifesaving surgery. They also describe the extremities which result.

It would seem prevention is the only hope if no cure exists. Direct needle puncture of an artery is always hazardous. Perhaps needling of the carotids is not the best method of opacification for angiography. Arch injections by a catheter introduced into the ascending aorta through a right brachial arteriotomy provides more information by opacifing the origin and course of both vertebral and carotid arteries while avoiding injury to these crucial vessels. Open arteriotomy and proper repair assures patency of this vessel and eliminates the hazards of hematoma and tissue injection inherent in blind needling.

Arch injection requires sophisticated rapid film-changing devices providing serial films of the progress of the opacifying medium, but this, in turn, gives information regarding flow rates as well as luminal diameters.

Intravenous self-injection of paregoric does not seem to be the best way to handle the addiction problem. The human agony of these two case reports cries for a better solution. Iatrogenic aneurysmal abscesses can be avoided by a better method of carotid and vertebral angiography than blind needling of these major arteries for contrast injection. Egogenic aneurysmal abscesses illume the agony of addiction and urge a better understanding of human dependency.

N. Kenneth Jensen, M.D.*
Minneapolis, Minnesota

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*Clinical Associate Professor of Surgery, University of Minnesota.

Pyoderma Gangrenosum*

PYODERMA GANGRENOSUM is a well-established clinical entity consisting of noninfectious furunculoid lesions of the skin which rapidly break down and form ulcers that spread peripherally. Healing usually begins centrally in the lesions, and the scar, which is likened to the texture of cigarette paper, is characteristically soft and noncontractile. The clinical appearance of the lesions is distinctive, but occasionally the ulcers may be confused with those due to tuberculous, deep mycotic, or pyogenic organisms and to hypersensitivity to bromide or iodides.

Experience at the Mayo Clinic has shown that chronic ulcerative colitis is an associated finding in approximately 50% of cases involving pyoderma gangrenosum. Rheumatoid arthritis and rarely a vesicular eruption simulating dermatitis herpetiformis** may be present. The clinical course of the skin lesions is a chronic relapsing one, lasting several months or years, and spontaneous flares and remissions of the ulcerations are not uncommon.

The key to the treatment of pyoderma gangrenosum lies in the general health of the patient, particularly in the control of the chronic ulcerative colitis when present. My colleagues and I have found that the most useful drugs are sulfapyridine, sulfone derivatives, and oral corticosteroids. The choice of drug depends on the individual's response to therapy. Some patients with pyoderma gangrenosum are responsive to sulfapyridine but resistant to sulfones and vice versa. Also,

Continued

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*See page 22.
**See Test Your Word Score Page 97.

"All Interns are Alike"

It stands to reason. They all go through the same training; they all have to pass the same tests; they all have to measure up to the same standards; they all are underpaid, too. Therefore, all interns are alike.

That's utter nonsense, of course. But it's no more nonsensical than what some people say about aspirin. Namely: since all aspirin is at least supposed to come up to certain required standards, then all aspirin tablets must be alike.

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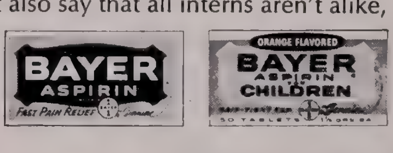
So next time you hear someone say that all aspirin tablets are alike, you can say, with confidence, that it just isn't so.

You might also say that all interns aren't alike, either.



unusually large necrotic lesions may heal only with large doses of corticosteroids, and such therapy may be lifesaving. At times, the administration of these drugs in combination, at reduced dosages, will effect better suppression of the disease and result in fewer complications from the drugs.

The two cases reported on by Altman and Mopper in this issue of MINNESOTA MEDICINE are examples of effective control of the disease by sulfones, although the presence of pyoderma gangrenosum is questionable in the second case.

The mode of action of sulfapyridine and sulfone in the control of pyoderma gangrenosum is not known. These drugs also are effective in the suppression of various noninfectious skin disorders such as dermatitis herpetiformis, subcorneal pustulosis, Weber-Christian disease, and acrodermatitis continua. Lorincz and Pearson have postulated that sulfapyridine, sulfones, and related drugs exert a therapeutic effect by combining or reacting with tissue or bacterial polysaccharides. Whatever the mechanism of effect, the therapeutic value and the requirement for maintenance doses of these drugs for long periods pose the problem of potentially serious side effects from these drugs. While generally less toxic, diaminodiphenylsulfone (Avlosulfon) is usually less effective than sulfapyridine. Notwithstanding its potential toxicity, sulfapyridine is the drug of choice for the majority of patients.

Sigfrid A. Muller, M.D.
Rochester, Minnesota

References

1. Altman, Jules, and Coleman, Mopper: Pyoderma Gangrenosum: A Report of Two Cases Treated With Sulfone Drugs. Minnesota Med 49:22, 1966.
2. Lorincz, A. L., and Pearson, R. W.: Sulfapyridine and Sulfone Type Drugs in Dermatology. Arch Dermat 85:2, 1962.

The Carcinoid Syndrome

THE REPORT by Zobl et al.* in this issue, concerning the circulatory and cardiac manifestations of malignant carcinoids, presents further data about this remarkable experiment of nature which has given us insight into metabolic, morphologic and clinical problems.

Cassidy described the first clearly recognizable example of this fascinating syndrome in 1930, but it remained only as a curiosity because of lack of a physiologic or anatomical background to which it could be related. In a quarter of a century the studies of Ersparmer on the enterochromaffin system of invertebrates; Rappoport's studies on serum vasoconstrictor (serotonin); Lembeck's isolation of serotonin from an intestinal carcinoid, and Barter and Pearse's demonstration that the granules of the Kulschitsky or enterochromaffin cells of vertebrate small intestine contained a serotoninformaldehyde complex made possible the remarkable synthesizing hypothesis of Thorson et al., in 1954, that serotonin, chemically 5-hydroxy tryptamine, produced the anatomical changes and clinical symptoms of patients with metastasizing carcinoids. When in 1955, Waldenstrom and Ljungberg demonstrated high serum serotonin levels in patients with the carcinoid syndrome, this hypothesis seemed almost proven.

Data have accumulated from about 200 reported cases of the syndrome. Most originated from primary small intestine tumors, but about two dozen were of bronchial origin and some arose from carcinoids in ovarian or testicular teratomas. The early indications that excess serotonin secretion would fully explain the syndrome have faded. Such modifications of the original hypothesis that only free rather than total serum serotonin was active; that factors involving release of serotonin were important; that the site of metastasis was a determinant or that variations in the amount of pulmonary monoamine oxidase, deaminating serotonin, were significant, have not sufficed. One of the strongest objections to the simple serotonin hypothesis has been the failure of numerous investigators to produce experimentally the characteristic heart valve lesions.

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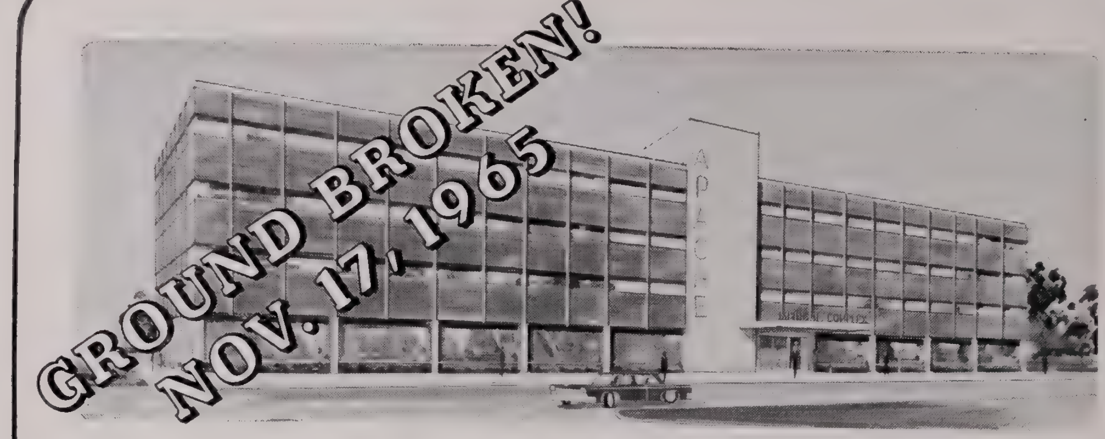
*See page 39.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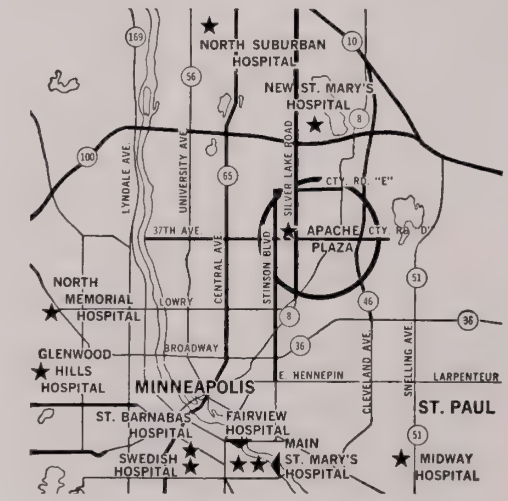
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Evidence has accumulated to indicate that the argentaffin* or enterochromaffin cells and carcinoid tumors derived from them contain substances other than serotonin that may be involved in producing the syndrome. Catecholamines (adrenalin and noradrenalin), histamine and serotonin analogues have been demonstrated in the tumors and in serum, and their implication in the syndrome suggested. Ascorbic acid has also been demonstrated in the tumors. The work of Oates et al., suggesting that carcinoids contain undefined substances which may activate kinins to form bradykinin, and the histochemical studies of Lillie and Glenner indicating the presence of ill-defined lipids and other substances in the cells of carcinoid tumors, give promising leads. Electron microscopy has demonstrated a distinctive appearance with neurosecretory granules resembling those of neuroblastoma and paraganglia. An adequate synthesis of these interesting possibilities is still to be made.

A number of uncommon associations of the carcinoid syndrome are intriguing. They include other endocrine abnormalities such as acromegaly, Cushing's syndrome, hypoglycemia, parathyroid adenomas and the pluriglandular adenomatosis syndrome. Most of these involve bronchial rather than intestinal carcinoids. Reports of oat-cell carcinomas secreting serotinin or associated with the carcinoid syndrome indicate that some bronchogenic carcinomas may be undifferentiated carcinoids.

It is evident that many permutations and combinations of this experiment of nature will be observed in the future. Investigation in depth by sophisticated modern techniques may unfold new chapters in physiology, pharmacology, anatomy and clinical medicine.

Leo Weiss, M.D.**
Minneapolis, Minnesota

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*See Test Your Word Score Page 97.

**Director of Laboratory, Mount Sinai Hospital.

Letter to the Editor:

Two deaths are reported under regional block anesthesia.* During my ten years with Dr. R. E. Farr and the many years that I used local anesthesia, we made it mandatory that when the point of the needle was stationary, the plunger of the syringe should be aspirated in order to be sure that the needle point was not in a vein; also, the needle was kept in motion. This is particularly imperative in the region of the board ligament where large veins are abundant. Though the quantity of the drug used is of great importance, far more important is the technique of its injection. We found by experimentation in animals that the intravenous injection of procaine is most hazardous, but that, in our experience, procaine was adequate and safe when properly used. I have had no experience with Cyclaine or Xylocaine.

I recall an operation on a foot by Dr. Farr under intravenous novocain anesthesia with a tourniquet control. The patient immediately showed toxic symptoms which stopped at once when the tourniquet was adequately tightened.

I compliment Drs. Freeman, Barno, and Baken on an excellent and important contribution.

Stanley R. Maxeiner, Sr., M.D.
Minneapolis, Minnesota

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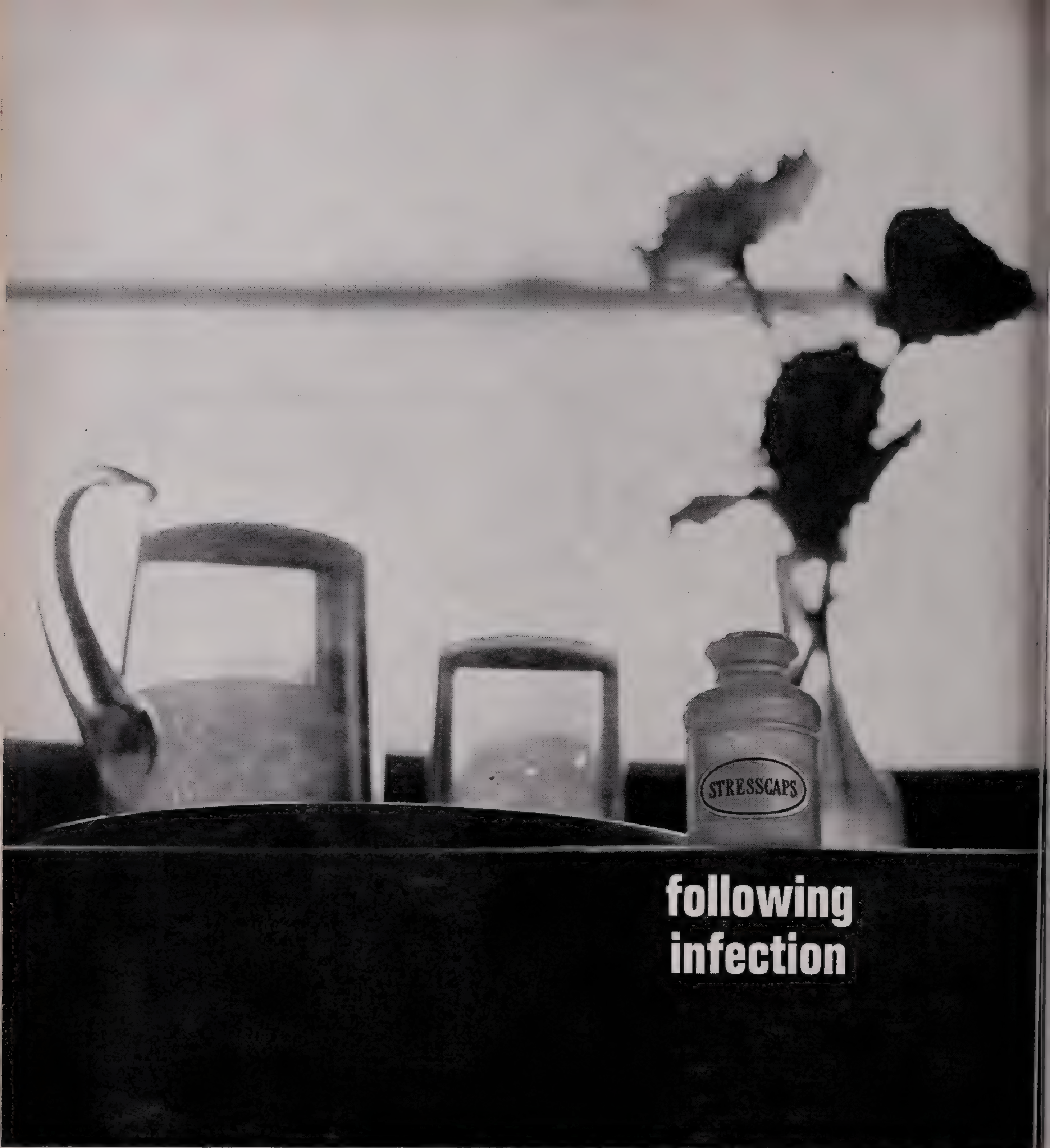
*Maternal Mortality in Minnesota due to Anesthesia. Minnesota Med 48:1231, 1965.



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Test Your Word Score

Obtunded — *made insensitive to pain* (page 11).

Collimation — *picking up gamma rays from radioactive substance injected previously* (page 18).

Berry aneurysms — *a small aneurysm of the cerebral artery communicating with the lumen of the vessel by a narrow channel* (page 27).

Catecholamines — *adrenalin-like substances* (page 39).

Geophagia — *earth eating* (page 59).

Koilonychia — *spoon shaped nail* (page 60).

Sideropenic dysphagia — *difficult swallowing due to iron deficiency* (page 60).

Mycotic aneurysms — *caused by microorganisms on the vascular wall* (page 89).

Herpetiformis — *resembling herpes* (page 91).

Argentaffin — *having affinity for silver salts* (page 93).

Ureteropyelocaliectasis — *dilatation of ureter and calyces* (page 122).

Chelating agent — *a chemical substance that forms a bond between a metal ion and two or more groupings of a single molecule* (page 171).

The Hippocratic Horoscope

When Hippocrates was called in on a medical case, he immediately had a horoscope drawn up for his patient's disease. This wheel, representing the stellar sphere, was sectioned into eight equal 45-degree triangular 'houses'; and on it, by accurate sidereal calculation derived from an ephemeris, were charted the sun, moon, and planets. Then from their relative configuration Hippocrates calculated the course of the disease from its inception through its crisis (or crises) to its termination; from this horological perspective he deduced what method of treatment to adopt. If the disease continued longer than one lunar cycle, he regarded it as no longer acute but as chronic, and therefore as requiring a new wheel. Hippocrates relied on horoscopes!

If children grew up according to early indications, we should have nothing but geniuses. — Goethe

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The Editor's Soliloquy

Etiology? — Physiologic!

Throughout medical history doctors have learned to treat diseases and their attendant symptoms long before the etiologic factors have become apparent. In the prescientific era the roster of suspected factors included enemy hexes and divine retribution; the phases of the moon and the conjunction of the planets; night air and swamp miasma; and more latterly, Grandfather's unabsolved sins.

Even in this supposedly myth-emancipated era of the Twentieth Century patients still continue to probe for causes. Before consulting their physician, they have inculpated some one event or constellation of events to account for their symptoms; they are reluctant to abandon their delusions and to accept academic explanations involving the complexities of pathologic anatomy, biochemical imbalances, embryological aberrations, congenital defects, and a host of other phenomena.

When confronted with irrefutable evidence that what she has is arthritis in the spine, sugar in the urine, cholesterol in the blood, or a tumor in the breast, is the female patient willing to accept physiologic malfunction as a cause? No indeed! She never had that before and is sure she doesn't have it now. Besides, she can't recall anything that could have produced such a sinister visitation!

There are many disorders and diseases for which we know no specific cause. Why do we grow old in body when our spirit remains young? Why does our hair turn gray and lusterless; why do we develop excrescences on our joints and on our vertebrae, keratoses on our back and pinpoint papilloma on our neck; why do we lose spots of pigment on our skin? Why are we stiff in the morning when we arise, when we work too hard, when we sit too long? Why does our neck or back ache after washing the ceiling, after ironing all morning, after driving the car for long distances? Why, after forty, does our blood pressure go up, our heart beat too fast, our hearing diminish, our vision shift, our gums recede, and our joints creak?

Why can't we keep the natural color and sheen of our hair, the petal freshness of our skin, the litheness of our body, the spring in our walk, the vibrancy in our voice, the stars in our eyes?

Why? — Let's face it! Inexorable physiologic age is catching up with us. Do we flout the idea of moderation: grow fat, get out of physical trim, do everything in excess? Is it not sufficient to know that burning the candle at both ends speeds up our physiologic time clock; and that these manifestations are not caused by an event, an incident; and that there may be no one but ourselves to blame — or to sue!

Carl O. Rice, M.D.

Mom says: It's nice to get up in the morning because your troubles haven't had time to get started.

The Mouse Amulet

For six thousand years the mouse has figured in medicine.

When, after the annual spring floods in ancient Egypt, the people saw mice emerging from the silt cracks of the fresh Nile deposit, they naively concluded that since the perennially revitalized soil produced the fresh crops on which they relied for sustenance, the mouse must incarnate the universal life principle, and hence that human consumption or application of the animal would transmit that vital force from mouse to man: a rational deduction from a fallacious premise.

Skinned, cooked, and eaten the mouse was apparently employed as a last desperate resort in terminal illness — especially for children in extremis. Ancient cemeteries in Egypt have yielded children's corpses — intact because of the dry sand in which they were interred — the stomachs and alimentary canals of which contained the remains of mice. Later scientific investigations have verified the practice in other areas of the East and in parts of Europe.

In Pliny's era also the belief prevailed that the mouse derived spontaneously from the Nile mud after each fresh inundation and was therefore a life-giver and a life-saver. Both Dioscorides of Greece and Abd er-Razzak of Algeria solemnly alleged that the ingestion of roasted mice would stop dribbling at the mouth in children, besides being a specific both internally and externally for multifarious ailments — from incontinence to warts.

The numerous papyri so ably translated by experts corroborate the therapeutic virtues of the "wee beastie." The Ebers Papyrus (1550 B.C.) prescribes mouse fat mixed with other miscellaneous fats for rheumatism. For healthier hair and to combat alopecia the Hearst Medical Papyrus suggests anointing the head with cooked mouse that has been allowed to rot in a mess of fat. The Erman Papyrus (1500 B.C.) advises that when a child is sick, either he or his mother eat a mouse and that the child then wear around his neck the bones of the same mouse bound together with a string in which seven knots have been tied.

For ulcers the Coptic Papyrus (800-900 A.D.) advocates a concoction of one ounce each of wax, santal,* pig lard, and chopped up mouse — all cooked together. Culpeper (1659) advised a three-day dose of powdered mouse for diabetics and those unable to hold their water.

Finally, in the Pharmacopoeia Universalis of one Dr. R. James, M.D. (1752), we are more fully apprised of the astonishing therapeutic versatility of the lowly mouse. "The whole Animal, and its Dung are used in Medicine. The Mouse, cut up alive, and applied, draws out Splinters, Darts, and Arrows, and cures the Bites of Scorpions, extracting the Poison. The Ashes cure the involuntary or nocturnal Flux of the Urine. The Dung purges Infants by Stool, is used in Clysters, cures an Alopecia, absterges Scurf from the Head, diminishes Stones in the Kidneys, or Bladder, and removes a Condyloma, Verruca, Ficus, Marisca, and the Tumors affecting the Anus."** Just like that!

The mouse myth persisted right up into the first quarter of the Twentieth Century in England and Wales, where flayed, fried, boiled or baked in a pie, the mouse was still relied upon to cure whooping cough, dribbling at

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*Santal: a compound extracted from sandalwood.

**Dawson, Warren, in The Journal of Egyptian Archaeology, Vol. X, 1924.

Continued to page 170.

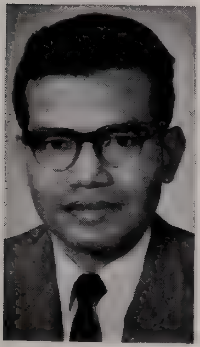
Our Contributors

. . . . from

Wayne State University
Detroit, Michigan

Jules Altman, M.D.

Dr. Jules Altman, born and educated in Europe, graduated from the University of Minnesota in 1958 where he interned. He trained at the Mayo Clinic in dermatology and is at present an instructor at Wayne.



Agustin Arbulu, M.D.

Dr. Agustin Arbulu was born in Lima, Peru, educated at San Marcus University, Lima, and received residency training in the United States in surgery. He is now Assistant Professor of Surgery at the Veterans Hospital, Dearborn, and is an instructor in the Department of Surgery at Wayne State.

Ernest Berkas, M.D.

Dr. Ernest Berkas, born in North Dakota, graduated from the Univesity of Minnesota in 1951, interned at St. Joseph in St. Paul. He completed his general surgical residency at Minneapolis Veterans Hospital and is Chief of Surgery at the Veterans Hospital in Dearborn and Associate Professor in the Department of Surgery at Wayne State.

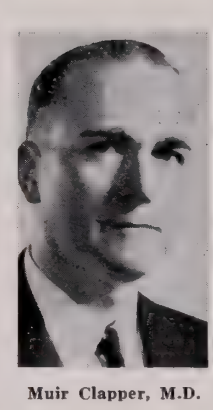
Continued

Richard Bing, M.D.

Dr. Richard Bing, born and educated in Europe, interned with Presbyterian Hospital, New York, and was a resident at Johns Hopkins. He joined the staff and left to be Professor of Medicine at Alabama, Washington University, St. Louis, and then departmental chairman at Wayne. He has lectured and published extensively on cardiac metabolism.

Jacob Chason, M.D.

Dr. Jacob Chason was born and educated in Michigan. He graduated in 1940 from Ann Arbor and received his pathological training in Michigan and at the Mayo Clinic. He is now acting Chairman of our Department of Pathology.



Muir Clapper, M.D.

Dr. Muir Clapper was born in Detroit, educated at Wayne State and received his graduate training in medicine at Receiving Hospital. He is now professor of medicine and has made a number of distinguished contributions to cardiology.

Alberto Cohen, M.D.

Dr. Alberto Cohen was born in Rio De Janeiro, educated in Brazil and is now in cardiovascular physiology at Wayne State University.

Dr. Ernest Gardner, born in the state of Washington and educated at their university, graduated from Stanford Medical School in 1941. He went into anatomy after his internship and became chairman of the department at Wayne in 1950. He is at present Dean of the Medical School and is the editor of a number of texts in anatomy as well as research papers concerning various aspects of connective tissue, bones and joints.

Ernest Gardner, M.D.

Dr. Paul Gonick was born and educated in New York. He received his M.D. from Yale in 1955 and was a resident at the Veterans and University Hospitals in Minneapolis in general surgery and urology. He is now chief of the section at Veterans Hospital in Dearborn and instructor at Wayne State. He has been interested in transplantation.

Paul Gonick, M.D.

Dr. Hubert Huebl was born in Montana, educated at the University of Chicago and Washington University, St. Louis, where he graduated M.D. in 1956. He interned at the Minneapolis General Hospital and was resident in Surgery first at Bellevue and then at Detroit Receiving Hospital. He is now an instructor in the Department of Surgery at Wayne State.

Hubert Huebl, M.D.

Dr. Alan Hymes, born in Minneapolis, graduated from the University of Minnesota Medical School in 1956, interned at Kings County, Brooklyn. He received his residency training at the Minneapolis Veterans Hospital in Surgery and is now a clinical investigator at the Dearborn Veterans Hospital studying cardiopulmonary bypass.

Alan Hymes, M.D.

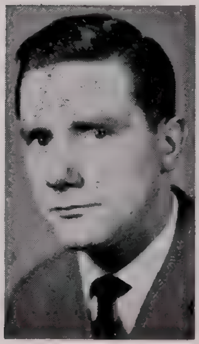
Continued

Leonard Kalfuss, M.D.

Dr. Leonard Kalfuss, born in Montreal, graduated from McGill University, interned at Toronto General Hospital. He is now a general surgical resident at Wayne State University.

James Landers, M.D.

Dr. James Landers, born in Nebraska, was educated at Washington University, St. Louis, and graduated M.D., 1953, from the University of Nebraska. He received graduate training in pathology at Henry Ford Hospital and at Wayne State University, where he is now Associate Professor.



Eide-Ditmar Lubs, M.D.

Dr. Eide-Ditmar Lubs was born and educated in Germany. He is now a research fellow in cardiac metabolism with Dr. Bing at Wayne State University.

Frank Monaco, D.D.S.

Dr. Frank Monaco was born and educated in Detroit, where he graduated D.D.S. from the University of Detroit in 1941. He is now director of the Department of Oral Surgery at Receiving Hospital and has published on problems in the treatment of maxillar facial disease.

Dr. Coleman Mopper graduated in 1942 from Georgia Medical School and was a resident at Wayne State Medical School. He is now clinical associate professor of dermatology at Wayne State.

Coleman Mopper, M.D.

Dr. Ananda Prasad was born in India, graduated from Patna University, M.D., in 1951, received a Ph.D. at the University of Minnesota in 1957 working in the Departments of Physiology and Medicine. He is now an associate professor at Wayne.

Ananda Prasad, Ph.D., M.D.

Dr. Raymond Read, 1946, Minnesota, received his surgical training in London, Boston and Minnesota. He was on the staff at the University of Minnesota before joining Wayne State in 1961.

Raymond Read, Ph.D., M.D.

Dr. Vish Sardesai was born in Goa, India, educated in Bombay and Wayne State where he graduated Ph.D. in biochemistry in 1962. He has been interested in the biochemistry of biologically active polypeptides.

Vish Sardesai, Ph.D.

Continued

Gordon Scott, Ph.D.

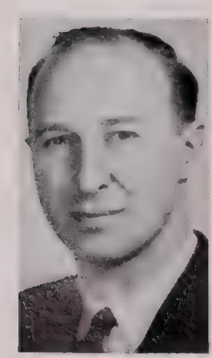
Dr. Gordon Scott, M.A. 1925, Ph.D. 1926, Minnesota, worked at Loyola, Rockefeller Institute, Washington, University of St. Louis and then was appointed chairman of the Department of Anatomy, University of Southern California in 1942. He came to Wayne in 1945 and was its Dean from 1950-1963. He is now Vice President for Medical College Development. He performed pioneering studies in the application of the electron microscope to medical research.

Walter Seegers, Ph.D.

Dr. Walter Seegers, born in Iowa, graduated from State University, Ph.D. 1934. He came to Wayne in the Department of Physiology in 1945, became chairman in 1946. He has received many distinctions and has published widely in the field of blood coagulation.

Allen Silbergleit, M.D.

Dr. Allen Silbergleit, born in Massachusetts, graduated from the University of Cincinnati Medical School in 1955, interned at the University of Minnesota. He was a resident in surgery at the Veterans Hospital, Minneapolis, and is now an instructor in surgery at Wayne State University.



Alan Thal, M.D.

Dr. Alan Thal, Chairman of the Department of Surgery, Wayne State University School of Medicine, received his surgical training under Dr. Wangensteen at the University of Minnesota 1952 to 1957, later joining the staff. He made distinguished contributions in the field of surgical sepsis, pancreatitis, and cardiovascular disease. He has recently developed an outstanding shock unit.

Dr. Arthur Vorwald was born in Dubuque, Iowa, where his father practiced. He was educated at the University of Chicago and Cambridge University, England, and has attained an international reputation in pulmonary pathology and problems connected with dust inhalation.

Arthur Vorwald, Ph.D., M.D.

Dr. Alexander Walt was brought up in South Africa and received his surgical training at the Mayo Clinic. He is Associate Professor of Surgery at Wayne, and Assistant Dean.

Alexander Walt, M.D.

Dr. Edward Zaleski, born and educated in Pennsylvania, graduated from Wayne State in 1959. He interned and was a resident in the Department of Medicine at Receiving Hospital. He is now an instructor with Dr. Bing.

Edward Zaleski, M.D.

Dr. Eldred Zobl, born and educated in Detroit, graduated from Wayne in 1954. He is chief of the cardiac catheterization laboratory at the Veterans Hospital in Dearborn and is interested in problems of cardiology.

Eldred Zobl, M.D.

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Curbstone Consultation

Ulcerative Colitis

QUESTION: In a patient who has suffered symptoms of ulcerative colitis for five years, with both X ray and proctoscopic evidence of the disease, would you recommend topical steroid treatment?

ANSWER: Although our experience indicates that 30% of patients with ulcerative colitis for five years or longer will not respond to this therapy, 60% of patients did respond and the majority of those responding did so both clinically and proctoscopically. Furthermore, when response occurs it is generally prompt. If no response was apparent in a week, I would add systemic steroid (preferably ACTH intravenously). If no response occurred within this week, I would stop the topical steroid. If the patient was acutely or desperately ill, I would begin therapy with topical and systemic steroids.

Marcel Patterson, M.D.
Associate Professor
University of Texas
Galveston, Texas

Fogging

QUESTION: Under the usual circumstances of mosquito control by the practice of fogging, is there sufficient danger of causing toxic effects to eliminate this practice?

ANSWER: Fogging for mosquito control does not result in any known hazard to health as the procedure is usually performed. The exposure is usually relatively brief. It may be a nuisance to those exposed to the insecticide but this nuisance must be weighed against the nuisance of the mosquitoes. An occasional person may have an adverse reaction to the spray procedure. This reaction may be somatic or functional and the differentiation may prove difficult. As a general rule, unnecessary exposure to pesticides should be kept to a minimum but the definition of "unnecessary" is one that cannot be decided without careful appraisal of the reason for the use of the insecticide.

Mitchell R. Zavon, M.D.
Cincinnati, Ohio

We fly in the air like birds; swim in the sea like fish. Wouldn't it be wonderful if we could walk on the earth like men? — Weslyan Christian Advocate

The Doctor and Literature

(Continued from page 73.)

Gillman, a physician at Highgate in 1816. Coleridge remained under the supervision of the understanding doctor until 1834. In those years, he wrote his finest literary criticism.

Today, many an ambitious man hires a Madison Avenue public relations expert to project a favorable image of himself to the public. Whether the socially acceptable image corresponds to the real man is immaterial.

The criticism levelled by Chaucer at the doctor of physik, by Shakespeare at the apothecary, and by Henry Fielding at the leech, so-called because the Eighteenth Century Doctor used those repellent creatures to suck infected blood from a patient, is not always favorable.

Hogarth, the Eighteenth Century Cartoonist, in a savage cartoon; *The Consultation of Physicians,* depicts twelve doctors with voluminous white wigs and gold-headed canes peering interestedly into the contents of a urinal. Hogarth believed most of the doctors of his time were quacks.

A Novel

A novel is a prose narrative of considerable length, which has plot, setting and characters. Novels of plot emphasize action; in them the characters are subsidiary to the working out of the action to a conclusion. An Agatha Christi "whodunit" has characters involved in the crime which is solved in the last chapter.

Any novel of prison life, whether Dostoevski's *House of the Dead* to Jerome Odlum's *Each Dawn I Die,* based on his imprisonment at Stillwater penitentiary, has only one plot: a prisoner does not like where he is and wants out.

In novels of character, the people in the story predominate over the plot which is frequently negligible. The Fat Boy in *Pickwick Papers,* Sherlock Holmes, Scarlett O'Hara, James Bond, 007 are more real to us than our next door neighbors; but the plots of the novels in which they appear are quickly forgotten.

(To be continued next month)

Reverend Edward Keenan
Minneapolis, Minnesota

Lizardry

Marcellus (5th century A.D.) advises: To stay colic one binds about the patient three times with an incantation a string with which a copper needle has been threaded and drawn through a (green) lizard's eyes, after which the reptile is released at the same point where it was captured.

In another passage Marcellus recommends the drawing by a silver needle of threads of nine different colors other than black or white through the eyes of a new-born puppy before they open, after which the puppy is to be thrown into the river.*

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*Thorndike, Lynn: A History of Magic and Experimental Science, Vol. 1, p. 590. The MacMillan Company, New York, 1923.

X-ray Conference

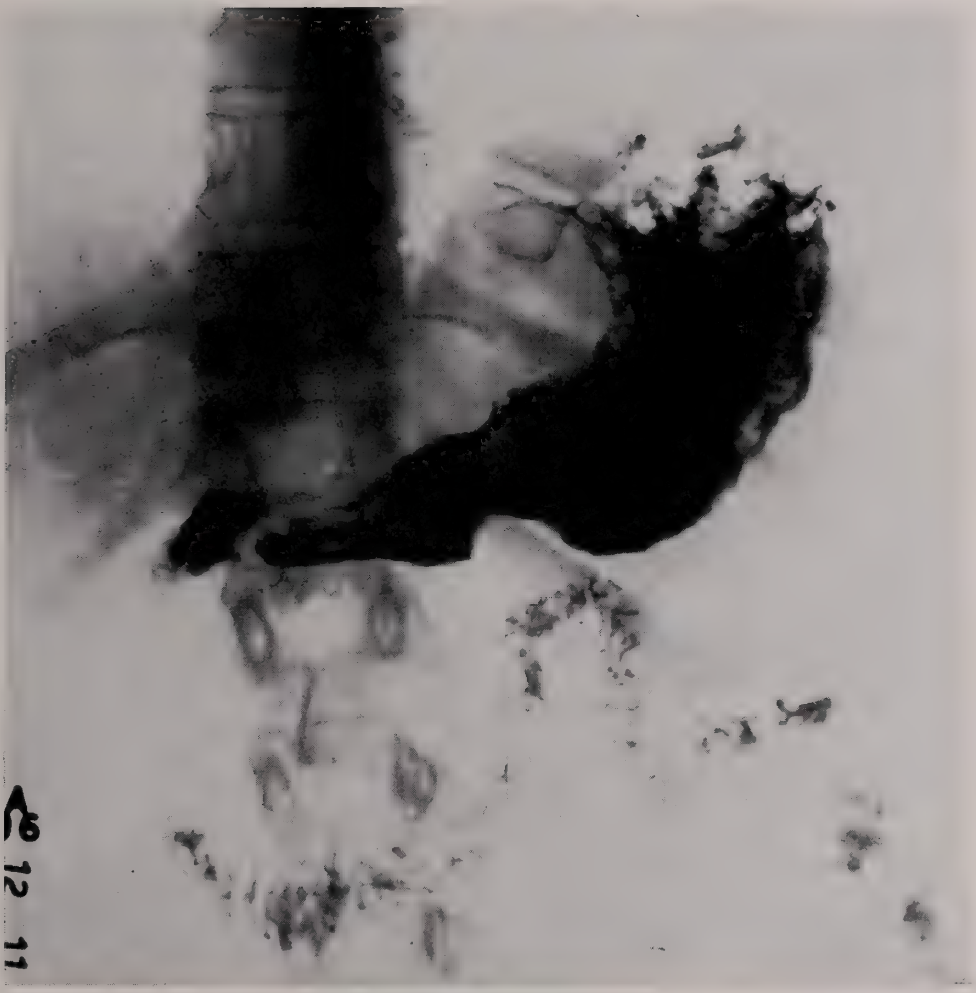

Figure 1

This forty-nine-year-old man was hospitalized with a three-week history of epigastric pain, vomiting, anorexia, weight loss, and pedal edema.

Roentgen examination of the stomach (Figure 1) demonstrated large, ineffaceable mucosal folds of the fundus and body. The gastric wall was thickened. No peristaltic activity was observed. The radiologist's differential diagnosis included lymphoma, carcinoma, chronic gastritis, Menetrier's disease, and recent gastric hypothermia (freezing).

What is your diagnosis? (See next page)

Diagnosis: Menetrier's disease.

Menetrier's disease is characterized by giant hypertrophy of the gastric rugae. The etiology is obscure. It has been seen in all age groups. The incidence is higher among males. Symptoms, if present, are similar to those of peptic ulcer. Many cases are associated with "weeping" of protein through the gastric mucosa leading to hypoproteinemia and peripheral edema.[1-3] This may be demonstrated by the intravenous injection of I^{131}-labelled polyvinylpyrrolidone (PVP). Leakage of its large molecules due to the exudative gastropathy will cause increased radioactivity of the feces.[4] Some patients harbor multiple endocrine adenomas.[5,6]

The roentgen picture consists of various combinations of the following findings: enlargement of mucosal folds, irregularity of the greater curvature, thickening of the gastric wall, and a peculiar reticular pattern produced by barium mixed with mucus.[7] Differentiation from lymphoma and carcinoma may be extremely difficult.

The patient present here had all the features of Menetrier's disease. His serum protein was 4.2 gm./100 ml. (albumine 2.6 gm., globulin 1.6 gm.). On surgical exploration the stomach showed huge mucosal folds, with microscopic evidence of elongation and increase in number of gastric glands. An islet-cell adenoma was found in the pancreas.

S. H. Tsai, M.D.
Department of Radiology
Hennepin County General Hospital

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On Coral

Thirteenth century Vincent of Beauvais, in his enthusiasm over the therapeutic virtues of coral, claimed that it checked hemorrhage, reduced corpulence, drew harmful humors from the eye, cured ulcers, and benefited heart, intestines, and spleen. Suspended over the mouth it stopped stomach-ache; suspended from the neck it prevented epileptic fits.

Lynn Thorndike: A History of Magic and Experimental Science.

Fracture–Trauma Conference

Edentulism and Jaw Fractures

The problems of jaw fractures should never be considered from purely anatomical attitudes. The management of any fracture, simple or complicated, requires the restoration of function. Cosmetic restoration, desirable as it is, is not the primary objective in treatment. Many cosmetically acceptable post-treatment cases are unacceptable from the functional point of view. The patient becomes less enamored of his cosmetic status and more concerned about his functional disability.

The functions of the jaws are fundamentally those of mastication and speech. Mastication is accomplished by the dental apparatus which, properly considered, is a complex system limited not merely to teeth and periodontal structures. The jaws, the muscles of mastication, and the complex temporomandibular joint are all integral parts of the dental apparatus. The temporal and zygomatic bones are also intimately associated, and when these bones are involved in jaw fractures, they often interfere with the temporomandibular articulation and with free movement of the mandible.

Whenever the jaws are fractured there is disruption of the proper vertico-occlusal dimension.* The vertico-occlusal dimension becomes increasingly important in the complex injuries in which alveolar process fractures isolate the tooth-bearing portion from the main body of the bone. If the correct vertico-occlusal dimension is not re-established initially, the impaired function is demonstrated by subsequent temporomandibular joint and muscular disabilities. These problems are further compounded by malocclusion and improper arch symmetry.

Full Complement of Teeth

When either or both jaws are fractured and contain a full complement of teeth, it is relatively easy to accomplish an anatomical and functional reduction by immobilization of the jaws. In this instance, the teeth act as splints and can be interdigitated with minimal difficulty.

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*The vertical dimension of the face when the teeth (or substitute) are in central occlusion.

Continued

Individual Teeth

Any consideration of jaw function concerns the teeth individually and as a unit with multiple complex functions. Each tooth is encased in its own membrane and functions separately and in unison with its neighbors to help establish the jaws in proper functional and rest positions. Correct placement of the condylar head in the glenoid fossa is thus achieved. This concept becomes particularly important when jaws have to be immobilized for several weeks during the period of active osteoid formation. If the teeth, dental arches and jaws are not properly related, occlusal disharmonies result which cannot be corrected except by extensive new surgery. When individual teeth are fractured, lost, or displaced from their alveoli, the reduction becomes difficult and complicated. The management of such cases demands specialized dental knowledge.

Edentulism

When patients suffering from jaw fractures are totally edentulous, the management becomes even more complex. This is particularly evident when the patient does not wear dentures, or if the dentures are lost or beyond repair. These cases usually require open surgery with fabrication of properly designed splints to aid in the immobilization and reduction of the fractured jaws. The construction and placement of such splints requires the special knowledge of the dental discipline. It can be safely stated that in every case requiring splints of a dental nature, the splints must be regarded as substitutes for the missing teeth. Therefore, splints have to conform to the functions expected of natural teeth in establishing and maintaining the proper vertico-occlusal dimension. The purpose of this paper is to demonstrate how such splints are used to aid in the management

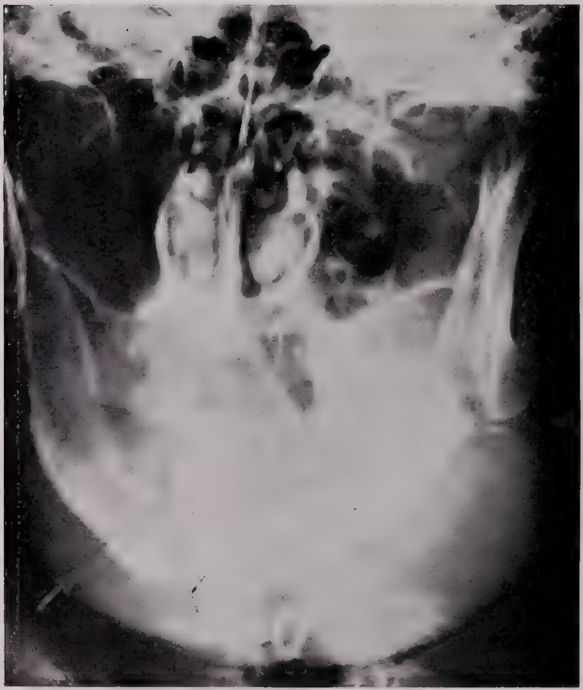

Fig. 1 — Note the obvious deformity of the body of the mandible with the proximal fragment displaced superiorly and laterally.

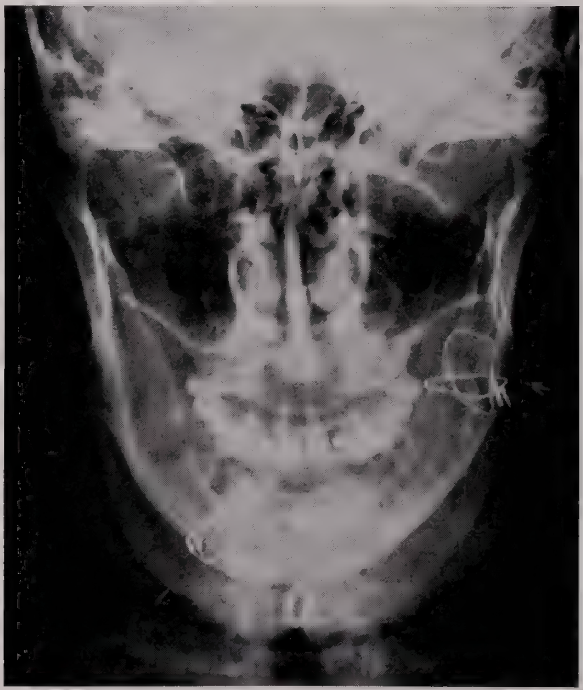

Fig. 2 — A good postoperative result with symmetrical continuity of the mandible adequately demonstrated. Note placement of wire sutures.

of the edentulous jaw fracture.

Three cases of total edentulism will be presented to illustrate the rationale and indications for the use of splints in the case of jaw fractures ranging from relatively simple to very complex.

Case Reports

Case 1

A 60-year-old negro man was struck on the jaw seven days prior to admission to Detroit Receiving Hospital. His physical examination on September 28, 1964, was within normal limits except for an obviously compounded, bilateral fracture of the mandible. His complaints relative to the jaw were pain, paresthesia of the inferior lip bilaterally, and dysfunction of the mandible. The radiographic study of the jaws demonstrated a bilateral fracture of the mandible with gross displacement (Figure 1).

Since the patient was wearing dentures which were functional, there was no need to fabricate new splints. An open reduction was performed on September 30, 1964, via the submandibular approach. The fractures were reduced and maintained in position by transosseous criss-cross wires.

The dentures were inserted on the first postoperative day and occluded in centric relation. This position was maintained by a Barton bandage which tended to limit and restrict the movement of the mandible without completely immobilizing it. The patient was discharged after one week of uneventful postoperative course.

The Barton bandage was removed six weeks after treatment, and follow up X rays taken thirteen weeks after original surgery revealed good anatomic symmetry (Figure 2). The patient functions normally in all masticatory movements.

This case demonstrates the application of the patient's dentures as splints to restore the proper vertico-occlusal dimension. It also demonstrates that complete and firm immobilization of the jaws is not always mandatory for every case of jaw fracture, but that adequate immobilization or limitation of movement produces good results. It is the opinion of the authors that some movement of the fractured mandible stimulates early osteoid formation. The open reduction and firm approximation of the fractured

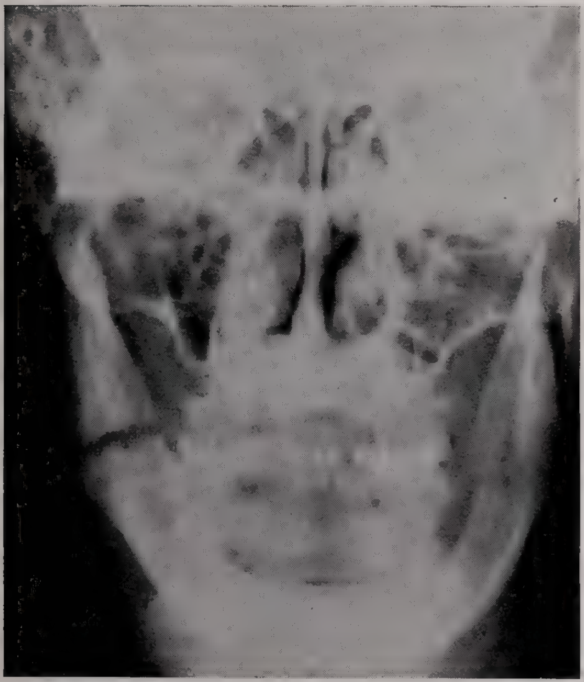

Fig. 3 — Note the laterally displaced proximal subcondylar fracture on the left, and the relatively undisplaced fracture on the right. (The patient is wearing a maxillary denture.)

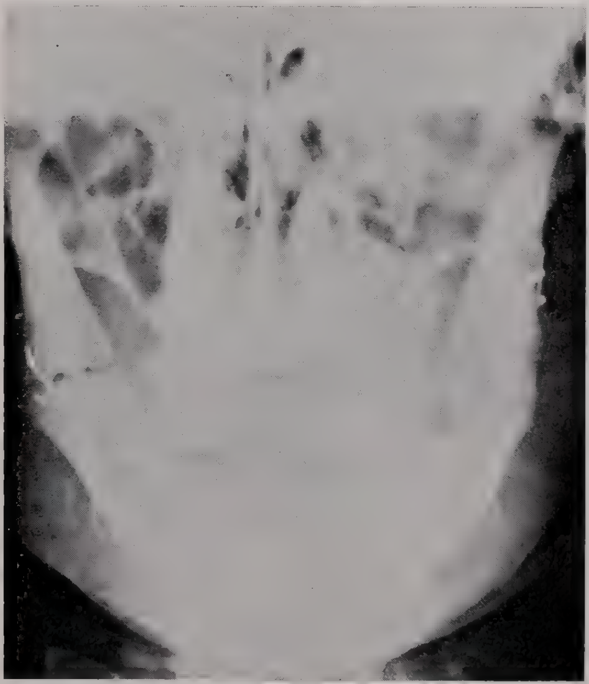

Fig. 4 — Postoperative result demonstrating splint application with four circum-mandibular wires. Note placement of wires in left subcondylar fragment with marked improvement of displacement.

Continued

parts by adequately placed transosseous wires resulted in a very sturdy anatomic mandible requiring minimal postoperative fixation.

Case 2

A 61-year-old negro man was beaten and robbed on June 27, 1964. He was examined at Detroit Receiving Hospital. The radiographs demonstrated fractures of the right angle and the left subcondylar process of the mandible (Figure 3). Laboratory findings were within normal limits and, except for the mandibular fractures, the physical examination was essentially negative.

Since open reduction was decided on as the treatment of choice, prosthetic splints were prepared prior to surgery. On July 3, 1964, a bilateral open reduction was accomplished via the submandibular approach, employing transosseous wires to maintain the fractured parts in anatomic relation. The mandibular splint was held in position by circumferential wires placed at the time of surgery.

One day after surgery the maxillary splint was inserted and the jaws brought into proper centric-relation and vertico-occlusal dimension by occluding the splints, with a Barton type cohesive gauze bandage employed to maintain this relation. The bandage was removed five weeks after surgery, and the patient was permitted to function on a soft diet.

An X ray taken seven weeks after treatment demonstrates excellent anatomic position (Figure 4). The mandibular splint was removed at this time, and it was noted that the mandible functioned normally in all excursions.

This case demonstrates the use of a maxillary denture and the fabrication of a mandibular splint, as the patient did not wear a mandibular denture. The problem in this case was the establishment of proper vertico-occlusal dimension, which was accomplished by fabrication of the splint to occlude with the maxillary denture which was the point of reference for this patient. This case also presents the additional problem of a joint fracture dislocation. The mandibular splint was wired to the jaw in order to accurately relate the mandible to the maxilla. This procedure permitted

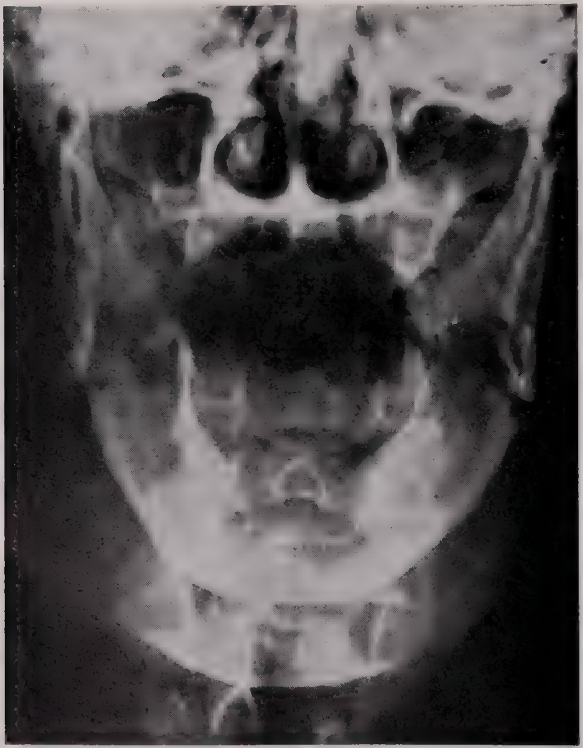

Fig 5 — Grossly displaced, bilateral, comminuted fracture of mandible. Note marked inferior displacement tending to give patient a chinless appearance.

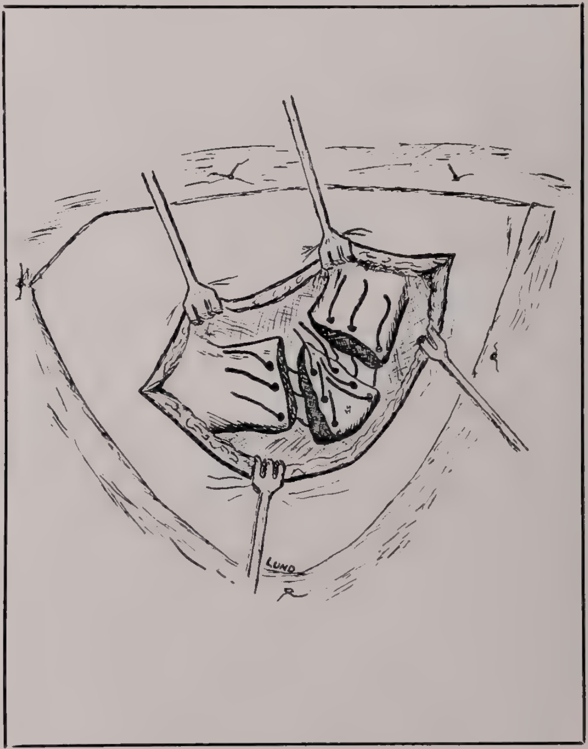

Fig. 6 — Schematic drawing demonstrating the technique of intraosseous wiring employed to replace free bony fragment (autogenous graft).

the jaw and splint to move as a unit without displacement of the mandibular splint. The result obtained indicates that this procedure was efficacious. There was adequate but not complete immobilization of the jaws. The purpose of slight movement was to institute more rapid consolidation of the fractured condyle and to prevent the possibility of ankylosis. It is considered good treatment to mobilize subcondylar fractures in three to five weeks.

Case 3

A 58-year-old white man was first seen in the emergency room at Detroit Receiving Hospital on August 23, 1964. The patient had been beaten six days prior to this visit. For the preceding 72 hours he had been unable to eat or speak because of the resultant edema.

On physical examination there were large hematomas and ecchymosis present bilaterally on the face. The past medical history was noncontributory.

Oral examination revealed a completely edentulous patient, with the fractured anterior segment of the mandible grossly displaced inferiorly.

Radiographic findings revealed multiple bilateral comminuted fractures (Figure 5).

Nine days post admission, the edema had subsided and the patient went to surgery. Bilateral open reductions were performed. Because of the multiple comminutions the fracture reductions were difficult to accomplish. It was necessary to remove a fragment of bone from the operative field and drill six holes through it while it was supported on a board. Corresponding holes were drilled through the proximal and distal fragments of the mandible, and wires were passed through the holes in the free fragment. The fragment was placed in proper anatomic relation, and the free ends of the wires were passed through the corresponding holes in the proximal and distal fragments (Figure 6). The wires were tightened firmly into position, accomplishing an excellent reduction (Figure 7). The left side presented a similar but somewhat less complicated problem.

After the incisions were closed, the previously prepared splints (dentures) were inserted. The maxillary splint was held by circumzygomatic wires. The mandibular splint was maintained by circumferential wires. The jaws were immobilized by intermaxillary fixation in excellent position (Figure 8).

The patient was discharged two weeks post surgery to be followed at weekly

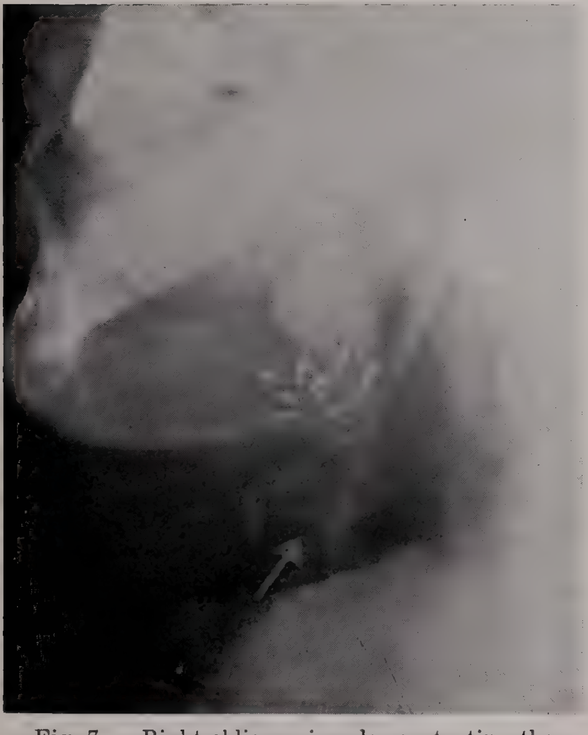

Fig. 7 — Right oblique view demonstrating the replaced bone fragment described in the text.

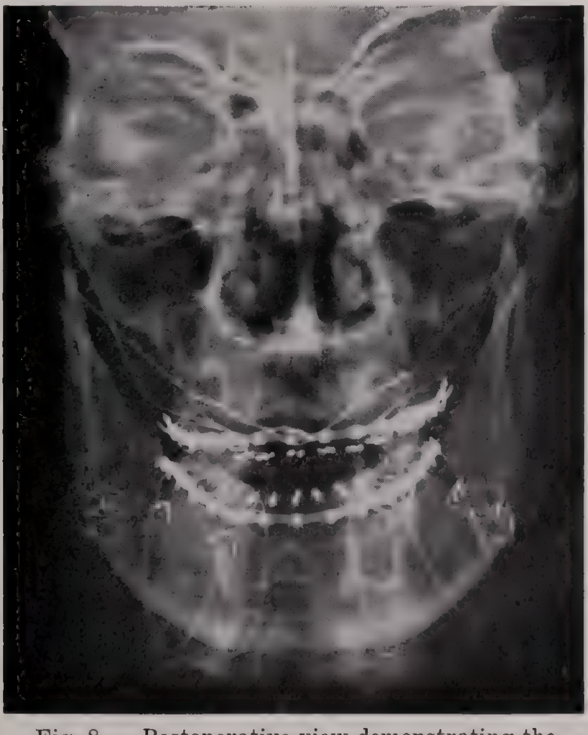

Fig. 8 — Postoperative view demonstrating the fixation of the splints to maxilla and mandible. Note the circum-zygomatic wires and the circum-mandibular wires.

Continued

intervals. The intermaxillary fixation was removed eight weeks after surgery, permitting limited function. After two weeks of limited function, the splints were removed.

Postoperative X rays taken five months later demonstrated excellent anatomical symmetry (Figure 9).

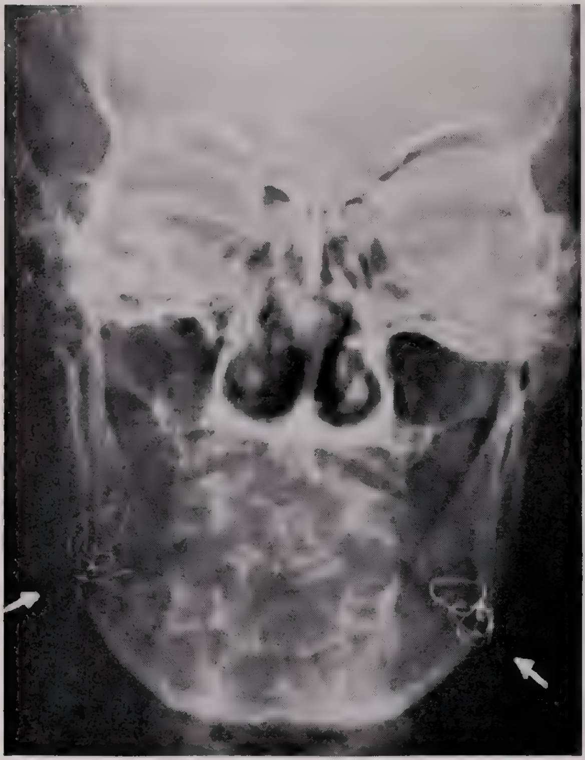

Fig. 9 — Radiographic appearance of the mandible five months after treatment. (Compare with Fig. 5.)

This case demonstrates the absolute necessity of complete and firm immobilization in order to assure a proper healing of the complicated fractures. In this case undue movement would be detrimental and tend to produce failure. Therefore, both maxillary and mandibular splints (dentures) were firmly wired into position to prevent movement. The efficacy of the procedure was demonstrated in the success of this case.

Comments

Patients with jaw fractures should be maintained on a high-calorie, high-protein, liquid diet with vitamin reinforcement. Antibiotics and oral-hygiene care are mandatory. The general systemic care of the patient is supported as necessary.

In Case 1 the prosthetic splints were placed without wiring because of the anatomical reduction obtained and the relative simplicity of the fractures. Adequate immobilization and vertico-occlusal dimension were maintained with craniomandibular fixation. In Case 2, in order to maintain the continuity of the mandible and the proper centric relation, it was necessary to employ circum-mandibular wiring of the mandibular prostheses, thus enabling the mandible and the prostheses to move as one unit. The counteracting forces supplied by the muscular attachments were circumvented by interdigitation with the maxillary denture. This procedure accomplished stabilization of the more fragile condylar fracture. In the third case, certainly complicated by the gross comminutions with the necessity of a free autogenous graft, it was deemed mandatory to wire the maxillary and mandibular dentures into position. This maneuver accomplished a complete and accurate interdigitation of the dentures and immobilization of the jaws, thus insuring a greater probability of success.

Conclusions

In summation it can be stated that to prognosticate favorable results in edentulous jaw fractures the following principles must be maintained:

Maxillary and mandibular prostheses must be constructed to maintain the proper vertical-occlusal dimension.

Anatomical osseous relations must be maintained, when an open reduction is employed, by adequate transosseous wiring.

Proper immobilization of the jaws is mandatory for a sufficient time to allow for the proper osteoid formation.

Good oral hygiene and supportive therapy must be maintained.

It has been our experience that failures in treatment of edentulous fractures can be directly attributable to a failure to observe one or all of the aforementioned principles. All four outlined steps are equally necessary and important for the proper treatment of edentulous fractures. In general, adherence to the principles will produce proper postoperative function and good cosmetic results.

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Charles E. Reaume, D.D S.**
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Detroit, Michigan

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Virtues of Human Parts

From Pliny we learn that various parts and products of the human body are credited with remarkable virtues. A few instances of remedies drawn from the human body are ear-wax or a powdered tooth against stings of scorpions and bites of snakes, a man's hair for the bite of a dog, the first hairs from a boy's head for gout. Simply tying two fingers or toes together is recommended for tumors in the groin, catarrh, and sore eyes. Or the eyes may be touched thrice with water in which the feet have been washed. Scrofula and throat diseases may be cured by the touch of the hand of one who has died an early death, although some authorities do not insist upon the circumstance of early death but direct that the corpse be of the same sex as the patient and that the diseased spot be touched with the back of the left dead hand.*

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*Thorndike, Lynn: A History of Magic and Experimental Science, Vol. 1, p. 82. The MacMillan Company, New York, 1923.

The cancer with the highest incidence: skin. The cancer with the highest mortality rate: lung. Both, ironically, the most preventable of all cancers.

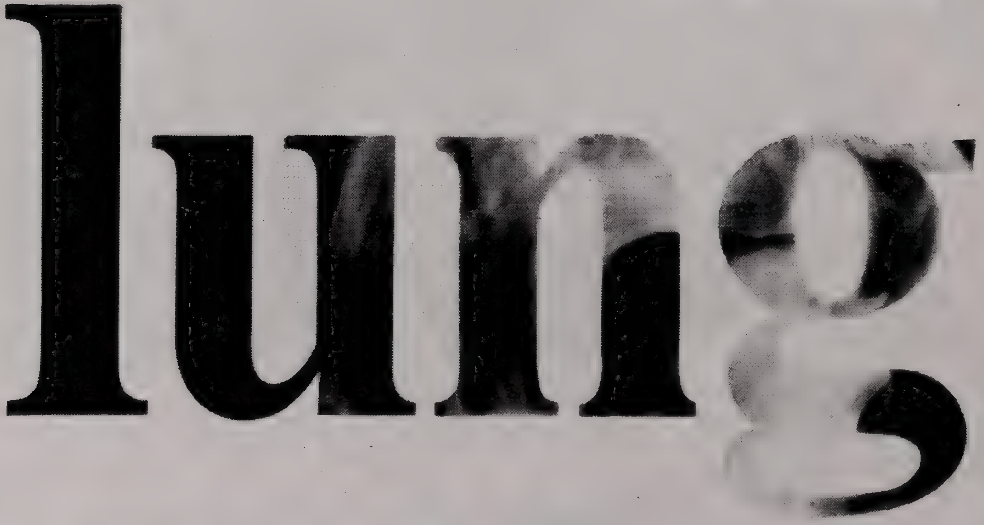
Lung cancer kills some 47,000 Americans every year. Estimates are that more than 75% of lung cancers are caused by cigarette smoking . . . a preventable habit.

About 80,000 Americans develop skin cancer each year. Since its principal cause is excessive exposure to the sun, preventive measures are clear.

Basal cell and squamous cell carcinoma, commonest forms of skin cancer, are easily cured in their early stages. The high incidence of skin cancer, the suffering, disability and disfigurement which too often accompany it, make it a challenging problem.

In its program of bringing vital facts about cancer to the public, the Society has two new films, both available for showing through any ACS Unit. WHO, ME? dramatizes the hazards of cigarette smoking. SENSE IN THE SUN urges both sun workers and sun worshippers to exercise caution. Like all Society films, their object is to save lives and diminish suffering from cancer by giving forceful expression to many of the facts about cancer with which you, doctor, guide your patients.

american cancer society ®



Tumor Anomaly Conference

Reflux in a Blind Ending Ureter: Experiment of Nature

The investigation of all cases of pyuria in the male is one of the cardinal principles of urology. The trail may often lead to the more common conditions of prostatism, stricture, or calculus disease, but on occasion unexpected and oftentimes puzzling conditions are discovered.

Case Report

A 56-year-old man entered the hospital with dull recurrent left flank pain of 25 years' duration. He was first seen in 1962 with similar complaints. At that time he

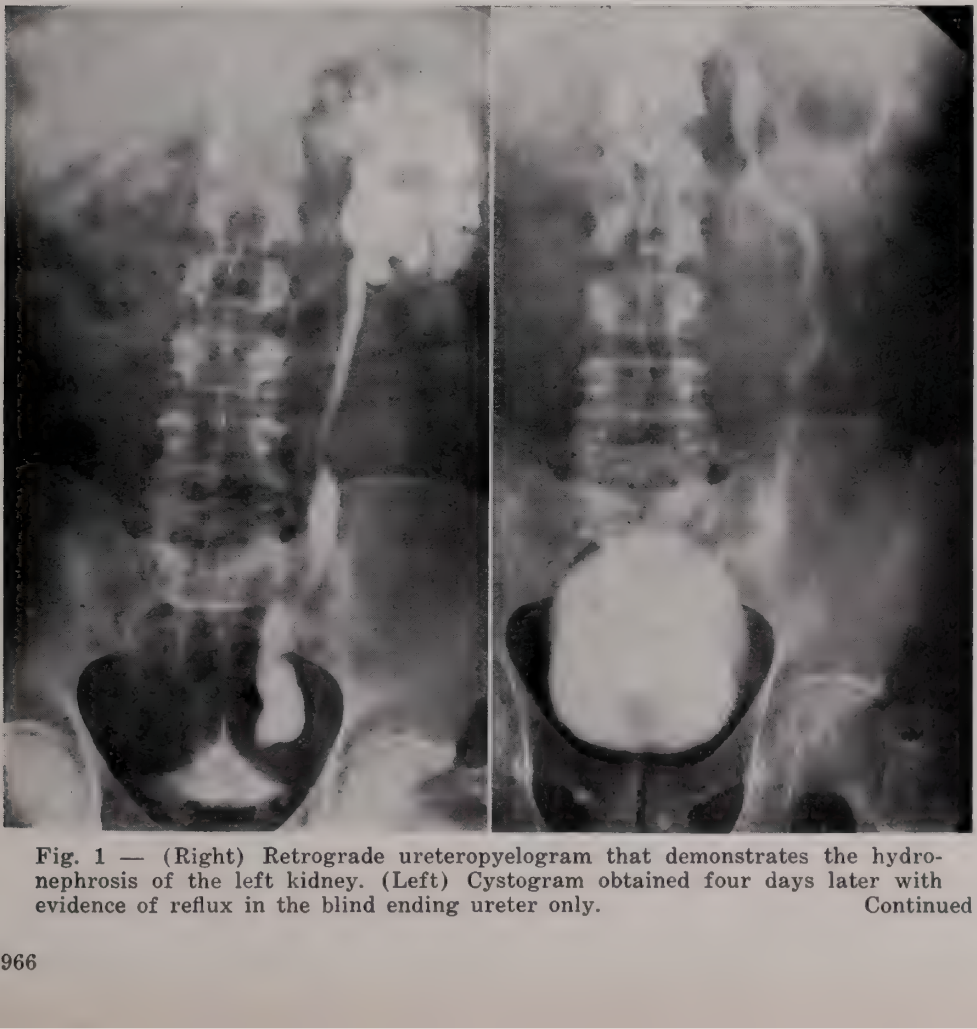


Fig. 1 — (Right) Retrograde ureteropyelogram that demonstrates the hydronephrosis of the left kidney. (Left) Cystogram obtained four days later with evidence of reflux in the blind ending ureter only.

Continued

had marked pyuria with a B. proteus isolated from the urine. An excretory urogram showed duplication of the right ureter and pelvis and nonvisualization of the left kidney. The patient refused further diagnostic procedures at that time, but returned two years later with identical complaints and submitted to further diagnostic studies. An excretory urogram was similar to the one done previously. A cystogram (Figure 1) showed reflux up a left ureter to the pelvis without visualization of calyces. Marked left ureteropyelocaliectasis* was demonstrated on retrograde ureteropyelograms. At the time of cystoscopy no evidence of vesical outlet obstruction was noted. Single right and left ureteral orifices were observed. However, the left was more patulous than the right. A B. proteus, resistant to all antibiotics, was isolated in the urine from the left kidney and from the bladder. Renal function studies were within normal limits. A nephroureterectomy was recommended, but the patient decided to postpone this until a later date.

Three months later the patient returned, and an uneventful left nephroureterectomy was performed. The specimen (Figure 2) showed two dilated thickened ureters, one terminating in an area of fibrous thickening at the upper pole of the kidney, the other in the renal pelvis. The major portion of the parenchyma was thinned, varying from 0.3 to 1.0 cm. Histologic examination of the upper pole showed an area of fibromuscular tissue containing a few scattered tubules, while in the rest of the kidney there was evidence of chronic pyelonephritis. The final diagnosis was renal agenesis of the upper pole of the kidney, double ureter, and hydronephrosis with chronic pyelonephritis.

The patient was discharged with a two-week supply of nitrofurantoin, and on return one month after the nephrectomy he had only occasional white blood cells per high power field in his urine.

When the left kidney was examined and compared to the roentgen studies, it was evident that the reflux demonstrated was present in the blind ending ureter only. This occurred at low pressures as well as high pressure since opacification of the blind ureter (in retrospect) was noted on at least one of the excretory urograms when the bladder was only partly filled.

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*See Test Your Word Score Page 97.

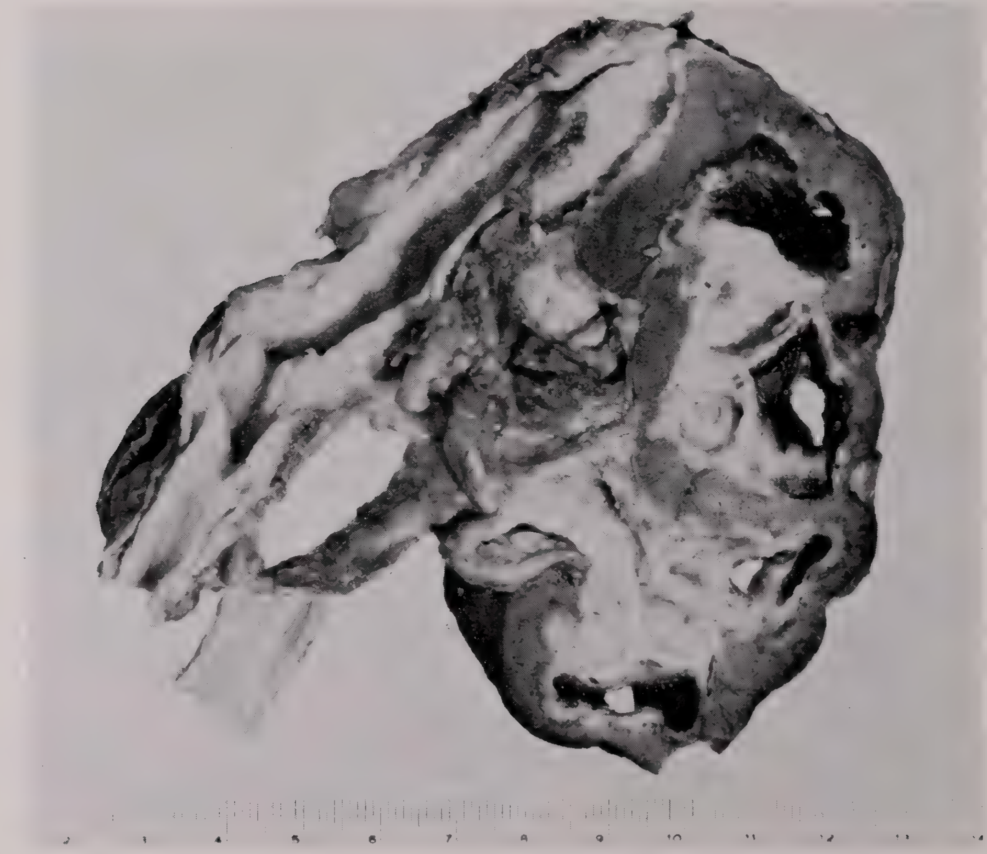

Fig. 2 — Section of the gross surgical specimen. The upper ureter ends in an area of fibrous thickening, while the lower ureter communicates with the renal pelvis and calyces.

Discussion

Ureteral duplication has an incidence of about one in 160 persons with complete duplication present in one in five hundred, and bilateral complete duplication present in only one in three thousand people.[1] Blind ending ureters are even less frequent.

It is axiomatic that the anomalous organ is more prone to disease than the normal.[1] However, it is of interest to speculate why the case presented developed reflux in only one of four ureters.

The ureterovesical sphincteric action has been ascribed to its submucosal length of the ureter (flap valve theory of Sampson[2]), its muscular coat[3] and its intramural length, and the flexibility and fixation of its lower border.[4] The controversy over the pathogenesis of reflux still rages, with advocates of infection, congenital abnormality of the ureterovesical junction, vesical outlet and urethral obstruction, and neuromuscular dysfunction providing additional data for their individual viewpoints.

If one or more of the above reasons for reflux are to be accepted as valid in this case, it must explain why three of four ureters did not reflux and why duplicated ureters with a single orifice should demonstrate reflux in only one of these ureters. Infection alone cannot be blamed for the reflux since it was present for many years; yet reflux was not demonstrated even in the ureter connected with the dilated, infected kidney and pelvis. No vesical outlet obstruction could be demonstrated, and even if it were present, it could not explain reflux in only one of four ureters.

It is doubtful whether the length of the submucosal segment of ureter plays any role in this patient's reflux, since both ureters had the same orifice opening into the bladder.

The only remaining reasonable possibilities are that there was a neurological, muscular or combined neuromuscular defect in the vesical segment of the blind ending left ureter, permitting reflux of urine to occur. Previous reports of similar cases of duplicated ureters by Stephans[3] have led him to emphasize the importance of the intrinsic sphincteric ureteral musculature in the ureterovesical "valve" mechanism.

Unfortunately the difficulties involved in demonstrating neurones in the ureter make this avenue of explanation of reflux hard to prove or disprove. However, the possibility of a neuronal defect does exist and must be considered in this case.

Summary

An interesting case of persistent pyuria with reflux in a blind ending ureter is presented. The various possibilities as to the pathogenesis of the reflux are discussed, and the conclusions reached are that a neuronal, muscular, or combined neuromuscular defect is the most reasonable explanation for the vesicoureteral reflux demonstrated.

Paul Gonick, M.D.*
Detroit, Michigan

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*Assistant professor in Urology, Wayne State University School of Medicine; Chief, Urology, Veterans Administration Hospital, Dearborn, Michigan.

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3-4 May be secured from the author or the reprints.

Papyrus Ebers[*]

On Bites

The ambit of pathologies catalogued in the Ebers Papyrus covers at least 82 supposedly common ailments in ancient Egypt, most of them all too deplorably familiar to us Twentieth Century mortals. To read a list of them is to so telescope space and time as to induce a close affinity of commiseration between us and those ancient Egyptian brethren of ours. After all, what else can so effectively make the whole world kin as headache, indigestion, constipation and coryza!

Bites further confirm our sense of consanguinity. Whereas our bites are more commonly dog or mosquito-inflicted, with the Egyptians the agents appear to have been crocodiles and — people!

"Three thousand years ago, we are forced to assume, bites from crocodiles were about as common as black eyes in these days; and to carry the simile still further, both were treated in the same way:

What to do Against the Bite of a Crocodile:

If thou meetest a Crocodile's Bite, and thou findest his flesh equally fallen away on both sides, so thou coverest it with Raw Meat the first day.

"A wound that merely demands a piece of raw meat to be clapped on it the first day could hardly be placed elsewhere than under Minor Surgery. Even a bite that one might suffer at the hands, or rather the teeth, of a lady or gentleman friend required more intensive treatment than that demanded by the bite of a crocodile."

Remedy Against the Bite or Sting of People:

Make thou for him a poultice of Raw Flesh on the first day. Afterwards treat him with Oil and Honey in order to do him good. Then put thou Oil in Wax in order to make him completely well at once."*

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*Bryan, Cyril P.: The Papyrus Ebers. D. Appleton and Company, New York, 1931, p. 67, and See Minnesota Med 48:1468, 1576 and 1694, 1965.

For Abdominal Troubles

Marcellus Empiricus (5th century A.D.) recommends pressing the abdomen with the left thumb and saying, "Adam, bedam, alam, betur, alem, botum." This is to be repeated nine times, then one touches the earth with the same thumb and spits, then says the charm nine more times, and again for a third series of nine, touching the ground and spitting nine times also.*

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*Thorndike, Lynn: A History of Magic and Experimental Science, Vol. 1, p. 592. The MacMillan Company, New York, 1923.

We cry loudly for a man of vision and when we get one we call him a visionary.

Athletic Injuries

Management of Head and Neck Trauma Secondary to Athletic Injury*

As participation in various athletic events increases at the grade-school, high-school and college levels, it is logical to assume that the number of related injuries likewise will increase. It is imperative that the team or local physician responsible for the care of these athletes has a thorough knowledge of the initial evaluation and, when necessary, the continued observation of a patient who has sustained an injury to the head or neck. Likewise, he will be responsible for making the decision as to when the injured person may safely return to athletic participation. The purpose of this summary is to lay down some guideposts which may be helpful to those individuals who, serving as team physicians, assume these responsibilities.

Many articles have been published reviewing the type, frequency and severity of athletic injuries.[1-4] Injuries to the head and neck fortunately comprise only a very small percentage of the entire number of injuries. It is signficant, however, that of the fatal injuries incurred, 50% are related to head and neck trauma. With careful initial care, observation, and recognition of signs of deterioration, many of these fatalities can be avoided if prompt definitive care is instituted.

Prior to engaging in competitive sports, the athlete should have a thorough medical examination. If a history of convulsive seizures is obtained, even if adequately controlled with anticonvulsant medication, he should not be allowed to engage in contact sports. Most seizures are probably related to previous cerebral damage either from trauma or disease processes. It seems only logical that such an individual should be kept away from situations wherein he would be subjected to further direct trauma.

Thorndike[4] has stated that if an athlete has a history of three or more concussions, he should not be permitted to engage in further contact sports. I would tend to agree with Murphey and Simmons' view: viz., that "each case is a highly individualized matter, and the exact severity of the brain injury has to be decided upon in each case."[2] If, after thorough investigation, no evidence of brain damage is found, it is probable that such an individual can engage in contact sports without any greater risk than those who have not had such injury.

Among those conditions which absolutely preclude participation in contact sports are: previous fracture dislocations of the spine, laminectomy for tumor or intervertebral disc herniation, arteriovenous malformations, intracerebral aneurysm, and all post-craniotomy states.

For purposes of classification, trauma to the head can be grouped into three categories.

The first and largest group comprise those athletes who, following direct

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*See Minnesota Med 48:1665 for fourth in this series. Sponsored by Minnesota Committee on Trauma of the American College of Surgeons.

Continued

or indirect head trauma, are momentarily "stunned," disoriented or unconscious. Such individuals usually quickly recover complete neurologic function, both physically and mentally. The great majority of such injuries are uncomplicated and a total recovery ensues. However, it must be remembered that extradural hematoma can occur after very minor trauma. Therefore I feel that *all* such injuries should be hospitalized and observed by trained personnel for at least twenty-four hours. If no hospital facility is available or the person refuses such care, an intelligent observer should watch him carefully for the next 24 hours. During this time the patient should be awakened every hour and note should be made of his orientation, the ease of arousal, motion in extremities, pupillary equality, and normalcy of pulse rate. If any deviation is noted he should promptly be re-assessed by the responsible physician. If the course following injury is uncomplicated, despite pressure from the athlete, coach, or family, this *patient should not engage in contact sports for at least one week.*[2] Slow, insidiously developing extra or subdural hematoma can occur days or even weeks following such injury.

The second group includes those individuals who have had some degree of cerebral contusion. These athletes have more than just momentary unconsciousness, and mental clearing is slow. It is not uncommon to find transient neurologic deficit, dizziness, persistent headache, nausea and/or vomiting. All such patients must be hospitalized and the previously mentioned careful, trained observation instituted. Skull X rays should be made. Any deviation from normal requires prompt emergency neurosurgical consultation. If the course is uncomplicated, *such athletes should refrain from participation in all sports for a minimum of two weeks.*[2] Thereafter, a careful re-evaluation should be made by the physician prior to permitting resumption of athletic activity.

The third group, the most severely injured, is made up of those athletes who are slow to regain consciousness, those with progressive neurologic deficit and those with depressed and/or compound skull fracture. There is no doubt that all these patients should be immediately hospitalized and, when necessary, transfer to a neurosurgical facility made without hesitation. If the patient is having acute respiratory trouble or is in shock, secondary to blood loss, correction of these situations should obviously be made prior to transfer. At the time of transfer a trained nurse or medical aide familiar with the use of suction apparatus and administration of O_2 should accompany the patient. Such patients should at all times have a free airway, as the use of oral airways and suctioning of excessive secretion can be of paramount importance. These patients should be transported on their side in order to minimize aspiration of vomitus and secretions. Narcotics are contraindicated in the early management of any head injury.

The prognosis for recovery in this third category of head injury is not as good as in the previous groups. However, with prompt initial care and intervention when necessary, the outlook has definitely improved. No matter how complete the recovery, *such athletes should be permanently barred from participation in all contact sports.*[2]

Cervical spine injuries of serious consequence may occur with participation in contact sports. The frequency of such occurrence is much less as compared to head injury. However, with the wide adoption of the protruding face protector on football helmets we may see increasing numbers of cervical spine injuries. The mechanisms involved in producing such injury have been extensively studied by Schneider et al.[3]

The clinical picture in cervical spine injury has wide variation, consisting of minimal pain and stiffness in the neck at one extreme to the tragic state of quadriplegia at the other. Again, as with head injuries, three broad groupings of cervical spine injuries may be discussed.

The first group comprises those individuals who have complaints of pain and stiffness in their neck without neurologic deficit. This is far and away the most common group that will be encountered. All such patients should have thorough X-ray study of their cervical spines in the anteroposterior and lateral views plus open-mouth views for the odontoid. It is imperative that the entire body of *all* cervical vertebrae be visualized. Occasionally it may be necessary to pull down on the arms at the time of the X ray to see the C7 body completely. Films that do not fulfill these stipulations are inadequate. It is surprising to see an occasional patient who, some days to even weeks following apparent minor injury to the neck, proves to have a fracture dislocation of his cervical spine without neurologic deficit.

If no abnormality is noted on the X rays, symptomatic, nonsurgical treatment is in order. Resumption of participation in athletics may then be resumed when a full range of motion of the neck is possible without pain or muscle spasm.

The second group comprises those individuals who have neurologic deficit. These people may have obvious weakness, or complain of numbness, or tingling in their extremities, particularly the arms and hands. The occurrence of such signs and symptoms should never be disregarded even though improvement appears to be taking place. One should treat *all* such injuries as potentially serious cervical spine fracture dislocations. These athletes should be transported on a stretcher or board with their heads held immobile. Mild head halter traction of 5-10 lbs. weight, when available, is excellent. Sand bags applied to each side of the head will help prevent lateral motion. Such transportation can be made in the supine position. However, if any complaints of nausea are present, transportation in the prone position (again employing measures for immobilization) is indicated. Someone should always be in attendance when these individuals are moved.

It is apparent that these athletes, even if roentgenographic studies are normal, have sustained significant trauma to the cervical spine. Even though complete recovery obtains, these athletes should *not* participate in contact sports and should be prohibited from diving.

The third group are those unfortunate people in whom paraplegia or quadriplegia is in evidence from the outset. The need for transportation to a neurosurgical facility is obvious and the previously mentioned mode of transport should be utilized. The prognosis for recovery unfortunately is extremely poor. A small percentage of these people will prove to have the syndrome of acute central cervical cord injury.[3] In that group recovery of lower extremity function occurs first, with a gradual ascending return of function that may be complete or only partial.

Summary

1. A brief outline for initial care and management of athletic injury to the head and neck has been made.

Continued

2. Certain general rules governing further participation in athletics have been set forth. It is emphasized that these should serve only as guideposts and that a good deal of individual variation exists.

Erich S. Wisiol, M.D.
Minneapolis, Minnesota

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Anglo-Saxon Leechcraft

For broken head, take betony: bruise it and lay it on the head above; then it unites the wound and healeth. Again, for the same: take garden cress, that which waxeth of itself, and is not sown; put it in the nose, that the smell and the juice may get to the head.

If the shanks be broken, take bonewort, pound it, pour the white of an egg out, mingle these together for the man whose shanks are broken. For a broken limb, lay this salve on the broken limb, and overlay with elm-rind, apply a splint; again, always renew these till the limb be healed. Clean some elm-rind and boil it thoroughly, then remove the rind, take ground linseed and brew it up with the drink of elm. That shall be a good salve for a broken limb.

If a man be wounded on the top of his head and the bone be broken, take sigelwherf (probably margold) and white clover plants and woodruff; put into good butter and strain through a cloth.

If the shoulder get up out of place, take the salve, apply a little warm with a feather; it will soon be well with the man.

For cancer take goat's gall and honey, mingle together of both equal parts, apply to the wound. Burn a fresh hound's head to ashes, apply to the wound. If it will not yield to that, take a man's dung, dry it thoroughly, rub to dust, apply it. If with this thou art not able to cure him, thou mayst never do it by any means.

For hare-lip, pound mastic very small, add the white of egg, and mingle as thou dost vermilion, cut with a knife, sew fast with silk, then smear without and in with the salve, ere the silk rot. If it draw together, arrange it with the hand; anoint again soon.

If a man's bowel be out, pound galluc (comfrey), wring through a cloth into milk warm from the cow, wet thy hands therein, and put back the bowel into the man, sew up with silk, then boil him galluc for nine mornings, except need be for a longer time. Feed him with fresh hens' flesh.

If thou wilt carve off or cut off a limb from a body, then look thou of what sort the place be, and the strength of the place, since some of the places readily rot if one carelessly tends them; some feel the leechdoms earlier, some later. If thou must carve off or cut off an unhealthy limb from a healthy body, then carve thou not it on the edge of the healthy body; but much more cut or carve on the whole and living body; so thou shalt better and readier cure it.*

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*Payne, Joseph F., M.D. Oxon.: English Medicine in the Anglo-Saxon Times, Oxford At the Clarendon Press, 1904, p. 84-92.

Neurological Conference

Difficulty Hearing and Seeing in an Elderly Patient*

Dr. Donald Soll:*

This 73-year-old-woman entered with the complaint of blurring vision and hearing loss of many years' duration. She has had a history of very small pupils for at least 30 years; nevertheless, her sight had been fairly good until she began to note increasing haziness of vision in her right eye about five years ago. As a child, she had considerable ear trouble resulting in the loss of her left ear drum and decreased hearing in both ears. This hearing loss has forced her to use a hearing aid for approximately the past 20 years. In recent years her hearing aid has been gradually less satisfactory.

History

The patient's past medical history is significant in that she has had a history of heart trouble and high blood pressure since 1963, which has been treated conservatively with diuretics, digitalization and nitroglycerin. Also she has had a mild diabetic condition controlled fairly well by diet. Interestingly, she was involved in an auto accident about 30 years ago and sustained a skull fracture on the right side of her head. Her mother died of stomach cancer and her father had arteriosclerosis. She has had no known venereal disease.

Physical Findings

Physical examination revealed a frail elderly woman weighing 86 pounds. She was quite alert but had difficulty hearing even with her hearing aid. Her blood pressure was 200/80 mm.Hg. and her pulse slow and regular at 52/minute. There was an absence of left tympanum; the right tympanic membrane was markedly sclerosed but intact. The remainder of the general examination was unremarkable except for a distinct bruit over the abdominal aorta.

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*Sponsored by the U. S. Public Health Service Grant N2502A63. These conferences are an integral part of the Comprehensive Clinic Program at the University of Minnesota Hospitals. The pediatric conferences are held every Wednesday from 1:00 to 3:00 p.m. The adult conferences are held every Thursday at 4 p.m. Co-ordinators for the project are Dr. Charles Branthaver and Dr. Edward De Foe, in Pediatrics, and Dr. Robert Soll, in Adult Neurology. Conference held May 27, 1965.

*Student doctor, University of Minnesota Medical School.

Continued

Neurologic Evaluation

On neurological examination the deep tendon reflexes were very brisk yet equal bilaterally, and plantar stimulation produced plantar flexion. Muscle strength, sensation, and coordination were likewise intact. The pupils were pinpoint and completely unresponsive to light or accommodation. A combination of mydriatics also failed to significantly dilate the pupils. A partial superior temporal quadrantanopsia was noted in the left eye during examination of the visual fields. The Rinne's test revealed a greater bone conduction than air bilaterally. The Weber test showed no lateralization.

Ophthalmological Findings

Ophthalmological consultation was obtained and the patient's visual acuity was found to be 20/70 without glasses and 20/60 with glasses in the left eye. The acuity in the right eye was less than 20/400 with or without glasses. Bilateral cataracts were noted, but these were not felt to account completely for the patient's decreased visual acuity. Early glaucomatous cupping was considered a distinct possibility.

Laboratory Determinations

Routine hemoglobin, blood count, and urinalysis were within normal limits. A two-hour postprandial blood sugar was 120 mg.%. The stool guaiac was negative. Several blood chemistries including serum proteins, cholesterol, and electrolytes were normal. A flat film of the abdomen showed calcifications, probably localized within the splenic artery and aorta.

An area of irregular calcification was found situated above the sella turcica on the skull x-rays, supporting the possibility of a brain tumor. (See Figures 1 and 2.) The electroencephalogram revealed bilateral central spikes and an intermittent slow wave focus in the left anterior temporal area compatible with a space-occupying lesion of focal atrophy, more

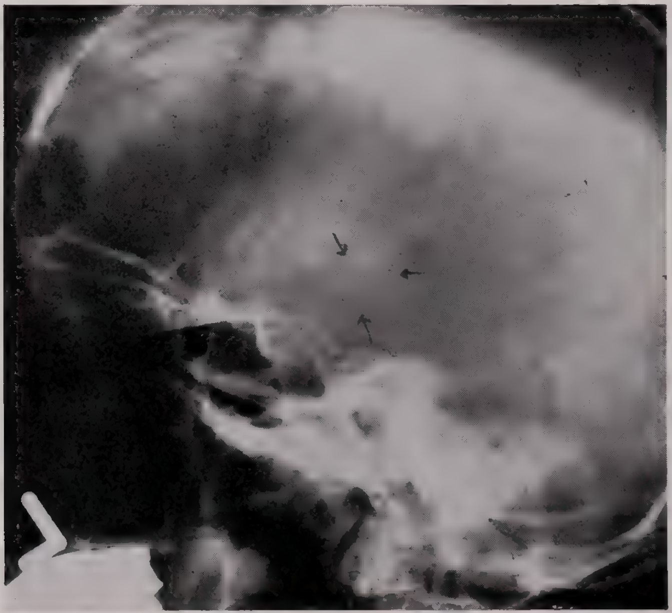

Fig. 1 — Lateral view of skull reveals a curvilinear calcification located slightly superior and posterior from the dorsum sellae. In both Figures 1 and 2, arrows point out abnormal intracranial calcification within the mass.

likely the latter. A brain scan was subsequently performed which was highly suggestive for the presence of an area of increased radioactivity in the suprasellar area.

Bone and nerve conduction were both reduced to such an extent that it was felt tympanoplasty would not benefit the hearing in the left ear. Neurosurgical evaluation considered a craniopharyngioma to be the most likely explanation for the x-ray findings on the skull films.

Dr. Roy Good:*

I have seen this patient for the past six or seven years, mostly for treatment of her cardiovascular problems. My primary reason for this referral was for evaluation of her visual problems, as she had complained to me that her vision had diminished sufficiently to interfere with her capability of reading and getting around the house. On cursory examination I felt that she was most likely developing a cataract.

Dr. Robert Soll:**

On neurological examination there were no objective findings that might further support the possibility of a brain tumor other than the visual field defect. The presence of suprasellar calcification on the skull x-rays did indicate, however, that this abnormality was a long-standing lesion, apparently causing little difficulty in previous years.

Our initial impression was that this represented an intravascular calcification within the intracranial portion of the carotid artery. The other possibility was a benign, very slowly growing tumor, which became much

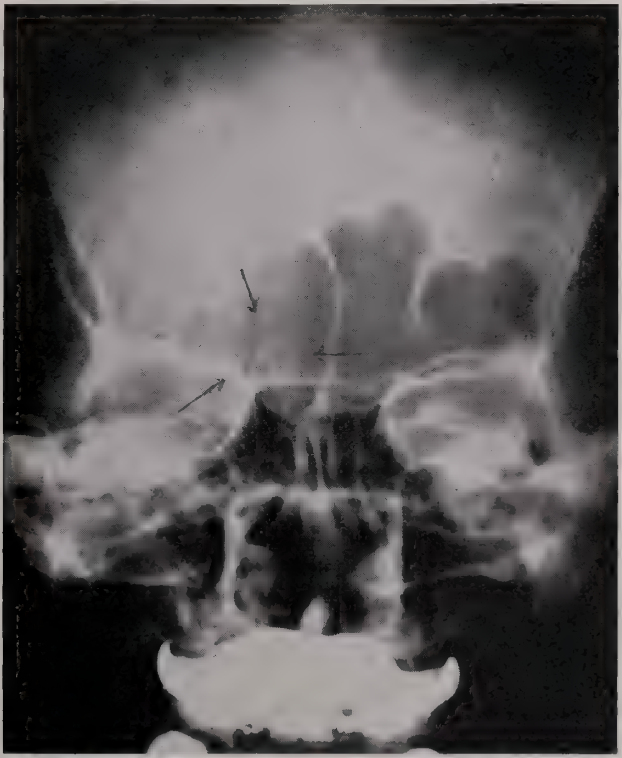

Fig. 2 — Anterior posterior projection of the skull shows more of an irregular calcification located to the right of the midline (outline by arrows).

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*Referring physician.

**Neurologist, University of Minnesota Hospitals.

Continued

more probable when the brain scan was noted to show a tumor stain in the same area.

Her pinpoint pupils quite likely have no relationship to this tumor; their cause must be attributed to some event happening at least prior to 30 years ago. In some animals, including man, the sympathetic supply to the iris courses through the middle ear by accompanying the tympanic branch of the ninth cranial nerve. Severe middle-ear disease could cause the destruction of this sympathetic supply and thus produce miotic pupils.

Miss Anne Seltz:*

The Audiology Clinic revealed that she had a severe degree of bilateral sensori-neural loss in addition to a bilateral conductive (middle ear) loss. The technique of masking the ear not being tested cannot be applied when the degree of hearing loss is severe. The patient understands speech better when her left ear is amplified. This could support a greater sensorineural loss on the right side.

The patient is presently wearing an on-the-body type of hearing aid. Our routine hearing evaluation includes judging the patient's ability to hear and understand speech with and without a hearing aid. It would be physically more comfortable for her to wear the ear-level aids; however, due to present-day limitations of hearing aids, she would probably be unable to receive sufficient amplification from the small instruments. Her inability to understand speech is not a result of a poor aid but of her degree of sensorineural hearing loss. What she hears is not only too soft but also distorted and unclear. The aid can only amplify sound.

Dr. Robert Soll:

The fact that the right ear drum is intact might imply that more damage had occurred to that ear due to the lack of adequate drainage. Dr. Brantner's* report of the patient's psychological tests reveals that her verbal IQ is 130. Her memory is excellent and there is no evidence for mental deterioration. A Graham Kendall test, which is a memory test for designs, and a Stanford Binet vocabulary test revealed that the patient's definitions of some words were the best given by anyone; for example, the word frustration was defined as "someone preventing you from doing something that you want very much to do."

Dr. John Brantner** knew that we were considering the possibility of her having a brain tumor. His conclusion from the psychological testing was that if she did have a tumor, it must be some type of benign, encapsulated, slow-growing tumor located in the frontal region of the brain.

Miss Helen Kretchmer:†

I saw the patient together with her two daughters. She is a little woman, nicely dressed, alert, and participating. She is one of twelve children. She was educated through the eighth grade and was married at 19. Initially she and her husband homesteaded one year in North Dakota; she was then advised by her physician to return to Minnesota because of her health. She has lived in her present home for over 35 years. Her husband was an oil dealer. Financially, they were comfortable and had a large home which she gave up at the time of her husband's death six years ago.

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*Department of audiology, University of Minnesota Medical School.

**Assistant professor of clinical psychology, University of Minnesota Medical Center.

†Supervisor and assistant professor social service, University of Minnesota Medical School.

The patient is an accomplished seamstress and has done upholstery work, slipcover and drapery making in her home. She was still doing some work as recently as last year. She now lives with one of the daughters. Her son has helped assist her financially. Her income derives from a $50 a month contract for deed from a piece of property left by a deceased brother plus the social security from her husband's employment, totaling approximately $100/month. Medical Aid for the Aged pays her medical expenses at home and she has county authorization for her care here.

The patient's apartment is in the downtown area convenient for shopping. Stairs are a problem for her because of her visual loss.

The patient has had as many interests as her physical capacity can encompass. She visits her family and travelled alone on the bus until recently. She is head of the devotions committee in church and belonged to a study club and a social club of which her husband was a charter member. She reads prodigiously and works crossword puzzles, to which she attributes her wide vocabulary. The books that she enjoys reading include Westerns, Perry Masons, and love stories. Living in a college town with its many social-cultural advantages, she probably has a broader life than many elderly people who live here in the city.

Dr. Charles Hewell:*

The importance of this patient's skull films is that they show a definitely abnormal calcification within the brain, apparent on the lateral view of the skull above the sella turcica. On an anteroposterior projection it is located to the right of midline. The lateral view gives this density a curvilinear appearance which would suggest the possibility of a vascular structure such as a tortuous vessel or a sacculated aneurysm. Another possibility is a slow-growing brain tumor. The reason that we have to say "slow" is because of the presence of calcification, and the fact that there is no evidence of chronic increased pressure. She has not decalcified her dorsum sellae, nor are the clinoids eroded.

There is an appearance on some views of an irregular rather than a curvilinear calcification, which could favor a tumor. An astrocytoma, oligodendroglioma, or meningioma would likewise have to be considered. Also, a craniopharyngioma would be another possibility; but the fact that it is not midline and that she is rather old is against this diagnosis. Furthermore, there is no tendency for craniopharyngiomas to calcify in the older patient as they do in children. The roof of the sphenoid sinus, the planum sphenali, appears to be pushed down on the right, which could mean that this structure is attached to a slow-growing tumor such as a meningioma.

A brain scan was done using a fast-acting isotope called Technetium which makes it possible to perform the test within an hour after injection. This patient's scan showed evidence of increased activity in the same region as the calcification, but I feel this is questionable. If the test is positive, it would favor some type of vascular tumor such as a meningioma or astrocytoma. The diagnosis probably could be made by angiogram.

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*Instructor, radiology, University of Minnesota Medical School.

Continued

Dr. Robert Soll:

Dr. Chou pointed out a technical difficulty from the neurosurgical point of view, due to the patient's frontal sinuses which are so large that the approach would have to be very high on the forehead, thus necessitating considerable canipulation of the brain in order to expose the tumor. There is also a possibility of infection from the sinuses.

Dr. Shelley Chou:*

Unless the patient is having a lot of trouble symptomatically, I would not be interested in doing an angiogram. We have evidence of calcification in the suprasellar area; we also know that she has some visual field change which is consistent with a suprasellar mass. It is conceivable that this could be an aneurysm, but from the visual field standpoint I think the probability is that this lesion is a tumor rather than an aneurysm. A craniopharyngioma may extend into the temporal lobe. I would not favor oligodendroglioma because it should show more of a stippled calcification than is present here, and this type of tumor is usually found in the frontal lobe. Regardless of whether she has an aneurysm, meningioma or a craniopharyngioma, I would recommend waiting. An angiogram would be nice to have, but cerebral angiography in this age group is not without risk.

Her symptoms are mostly visual and I would suspect that part of the problem is not related to the field defect but rather to the pupillary changes and cataracts. Therefore I would favor trying to correct these first. It is very unlikely that she will suffer much harm from the intracranial lesion. If it were to grow more, there is a slight possibility that she might develop signs of increased intracranial pressure because of obstruction of the ventricles.

Dr. Hewell:

Why doesn't she have evidence of long tract signs? Have you seen many craniopharyngiomas in this age group?

Dr. Chou:

First of all the lesion is sufficiently forward to prevent impingement on the pyramidal tracts; also, these tumors grow very slowly, thus permitting the brain and brain stem to accommodate to them.

Craniopharyngiomas are seen either in the very young patient, eight or 10 years of age, or in the sixty or seventy age group, skipping over the young adult and middle-aged patients.

Dr. Donald Soll:

The initial opinion of the ophthalmological consultant was that the patient had glaucoma, manifested by an appearance of cupping of the disc. After all tests for increased intraocular pressure proved negative it was felt that some optic atrophy most likely accounted for this appearance of the nerve head as well as for her decreased vision. Her visual acuity is only finger-counting ability in the right eye.

The possibility of cataract extraction has been considered for improving her vision. The ophthalmologists would like to re-evaluate the patient after using neosynephrine drops for two or three days in an attempt to get her pupils more widely dilated.

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*Associate professor, neurosurgery, University of Minnesota Medical School.

In conclusion, the following points can be made:

1. The patient should be followed but no further diagnostic tests made in regard to the intracranial lesion unless signs of increased intracranial pressure or other complications occur.
2. Another ophthamological evaluation should be obtained in order to determine if cataract removal will significantly improve her vision.
3. Hearing tests should be made to evaluate the possibility of her using binaural hearing aids to advantage.
4. The complete health status of the patient should be reviewed with her daughters, particularly emphasizing the above points.

Dr. Good:

I completely agree with this evaluation. If I had a choice, I would rather have her fitted with the appropriate aid to obtain good hearing than have the cataracts removed. I feel that it is much more important for a person of her age and intelligence to have adequate hearing for the exchange of information. In my experience, people with hearing losses are much worse off psychologically than those who are blind.

Robert W. Soll, M.D. Chairman
Adult Community Services
University of Minnesota

Participating in the conference were Miss Kretchmer, Supervisor and Assistant Professor Social Service; Student Doctor Donald Soll; Miss Anne Seltz, Department of Audiology; Dr. Shelley Chou, Associate Professor, Neurosurgery; Dr. Charles Hewell, Instructor, Radiology; Dr. Roy Good, Referring Physician and Dr. Robert W. Soll, Neurologist.

Experitissimum

Experitissimum was Gilbert of England's magical formula for treating epilepsy in the thirteenth century: At the first access of the disease, when the patient falls to the ground, all his clothes except his shirt should be removed and placed at his feet. The nails of all his fingers and toes should next be clipped and wrapped in a cloth. A long white thorn is then to be split and the patient dragged feet first through the cleft as far as his middle. The thorn should then be cut into bits and placed with the nail parings. Next the patient's hair should be cut in three places. These clippings of hair and the knife used in the operation are then to be added to the other paraphernalia wrapped in the cloth, and the whole is to be buried underground, and the following words uttered. In the patient's right ear, "Christ conquers"; in his left ear, "Christ reigns"; and to his face, "Christ commands."

Lynn Thorndike in A History of Magic and Experimental Science.

Every day the world turns over on someone who has just been sitting on top of it.
— Pageant

Life's taxi keeps on marking up the nickels, whether you are driving anywhere or just sitting still. — Cominco Magazine

Akhnaton

Was Akhnaton (Amenhotep IV), who ruled Egypt from 1375 to 1358, a victim of Froelich's syndrome, paleopathologists ask. Precise diagnosis from his remains is impossible, since the bones of the King were long ago partially crushed by the pressure of faulting rocks on his coffin; but study of the intact portions leads scientific observers to the tentative diagnosis of Froelich's syndrome: dystrophia and adiposo-genitalis. Careful examination shows delayed consolidation of the bones, slight hydrocephaly and acromegaly — with a somewhat feminine contour of figure.

Akhnaton was married to his half-sister, Nefertiti, who is said to have so markedly resembled him that as dressed-alike children they were hardly distinguishable. History records that he sired several daughters by Nefertiti; whereupon science asks: Could he have? and then replies: Yes — on the assumption that during his teens, the period when young Egyptians married, he was doubtless normal enough to have procreated, and that his sterility did not set in until his twenties or thirties.

Furthermore, artists have represented Akhnaton as normal in his teens but later as androgynous rather than wholly masculine: with a large head on a long thin neck, a receding forehead, a drooping chin, narrow shoulders, slim arms and legs, wide hips, and full breasts. Facially, some of his statues present either a fixed stare or a vacant smile.

To supplement evidence from the dead antiquity of remains and the static imagery of art one can turn to the more dramatic testimony of historical fiction. In Dmitri Merezhkovsky's "Akhnaton, King of Egypt" one can observe the man alive, during the most revolutionary and fateful years of his reign. His character appears highly admirable, his outlook humanistic, his objectives altruistic, and his devotion to those he loved warm and constant.

But unfortunately his insidious malady marred his private life and public career. Under the stress of excitement he became unstable and had occasional epileptic fits, "the sacred illness," so-called because it was thought to indicate possession by a god. He humbly considered himself stupid and deplored his forgetfulness. Sometimes he appeared to be in a trance; then again he became delirious and laughed and cried and sang.

Akhnaton was not the only historic personage so afflicted; other sovereigns were likewise visited by etiologically obscure disorders. Due to the practice of royal inbreeding, various hereditary diseases and defects have not been as rare in the annals of history as might be supposed. A full assessment of the impact of the morbidities of early monarchs might well clarify some of the more inscrutable aspects of their power-policies — not only politically and economically, but culturally and spiritually as well.

The field is wide open to the medico-historian.

There's a Difference

Actually there's only a slight difference between keeping your chin up and sticking your neck out, but it's a difference worth knowing. — News, Milford, Mass.

Child Psychiatry

Placement of Mentally Retarded Children Home or Institution?

For many years, planning for mentally retarded children frequently has raised the issue of whether or not a child should be placed out of the home for some form of care, education, or treatment. At times the issue has been one of whether or not the family can survive the strain of caring for a retarded child, who may present difficult management problems, or require complex nursing care. Occasionally the presence of a high degree of community pressure in the form of isolating or stigmatizing the family of the retarded child may be a factor.

Until recent years, when placement of a child out of the home has been deemed necessary for whatever reasons, the chief resource has been the state institutions for the retarded. Presently, however, in addition to the state schools and hospitals, there also exists a large array of facilities, including boarding homes, specialized private nonprofit institutions, and modified nursing homes. The actuality of the need for placement has been modified by the development of special education classes in the public schools for "educable" and "trainable" retarded children, and also, more recently by the establishment of privately operated state-subsidized Day Activity Centers.

The Minnesota State Department of Public Welfare has been directly or indirectly involved in the development of many of these facilities and programs. The direction of the state schools and hospitals is a responsibility of the Welfare Department Medical Services Division. The Medical Services Division's Section on Mental Retardation and Epilepsy discharges the responsibilities of the Commissioner of Public Welfare for persons committed to his care as mentally retarded. The Child Welfare Division is responsible for the standards and licensing of private institutions, foster homes, and Day Activity Centers for mentally retarded persons.

As awareness has increased of the enormous variety of medical, psychological, and social needs of mentally retarded children and their families, and as facilities have developed in response to these needs, decisions about care, education, and treatment have become extremely difficult to make. In an effort to provide some guidelines toward making these decisions, the Department of Public Welfare has issued a policy statement based on a few fundamental principles which may be expressed as follows:

1. Separation of a retarded child from his parents is an extremely serious decision with respect to the well-being of both child and parents.
2. Minimizing the effects of this often traumatic experience requires skillful and time-consuming work on the part of the family physician, pediatrician, and social case worker.
3. The decision to place a child out of the home should be a joint one, involving the parents, the family physician, and the case worker.

Continued

4. The determination of what facility to use should be based on a thorough medical, psychological, and social work study of the child and family, and a knowledge of the variety of facilities available to the child and family. This often requires the combined efforts of the pediatrician, psychiatrist, psychologist, social worker, and public health nurse.
5. If the child must be removed from his home, he should be placed in the facility closest to his home that can meet his needs.

The policies based on these principles are stated in a bulletin issued by the Commissioner of Public Welfare on July 26, 1965, as follows:

"1. No child should be considered for placement out of the home without a comprehensive evaluation not only of the afflicted child but also of the family and community resources. Ideally such an evaluation is coordinated and multi-disciplinary and includes pediatric, psychological, social, and psychiatric studies. Mental health centers, the Child Development Centers at Fergus Falls and Owatonna, the services of the University of Minnesota, and services still in the development stage can be utilized for this purpose, as can purchase of locally available service.

"2. Commitment to guardianship as mentally deficient is not a necessary or desirable step in all cases. A non-committed person is entitled to the same services as a person under guardianship. A person need not be committed as a prerequisite to admission to a state institution for mentally retarded. If commitment is desirable, it can be done at any time in the retarded person's life and need not be done when the retardation is first discovered.

"3. A final decision on placement should not be made until the parents have been told of the variety of facilities and services available and given the maximum opportunity to consider their feelings both about caring for their child who is retarded and about possible separation for shorter or longer periods of time. When separation is necessary in order to resolve a crisis, or to provide adequate nursing care or supervision, placement should be in a facility as close to home as possible to allow frequent contact between parent and child. Placement should not be considered as a permanent step.

"4. In an instance in which placement outside the home is urged that is considered inappropriate by the county welfare agency, such a placement should be discouraged until reasonable case work effort has been made to help the parents completely assess their situation. In some instances, a temporary placement may be necessary while case work continues. If the parents continue to insist on a long-term placement, a foster home placement is more desirable than institutional placement.

"5. Case planning for the retarded should be done as much as possible at the local level among those agencies that will be dealing directly with the person."

Each of these policies has a direct relationship to the general practitioner or pediatrician when he suspects or diagnoses mental retardation. The role that the physician takes under these circumstances may affect the entire family positively or negatively for many years.* The information about developments in the area of mental retardation has reached various professional groups slowly and unevenly. Parents, therefore, often are demoralized by contradictory statements from physicians, psychologists, and welfare workers even within their own communities regarding the desirability of institutional placement.

For example, until recently Down's syndrome (Mongolism) when discovered at birth has been understood to be adequate basis to insist that the afflicted child be placed in an institution immediately. Studies of such children, however, reveal that given the stimulus of parental relationships they may be capable of considerably more mental and emotional development than heretofore was realized. Although residential care may become necessary at a later age, the possibility of a more constructive adjustment is greatly increased if the child spends its early years in its own home. In the case of Down's syndrome, then, parents may be advised by the physician who delivered their child to apply for admission to an institution for the mentally retarded immediately. On contacting their county welfare agency, however, they may be told that such children will not be considered for admission until they are much older. From this point on, whoever they see may be unwittingly placed in the position of passing a judgment on the two advisors, but nothing that he says may really resolve the uncertainty of the parents. More subtle degrees of mental retardation or mental retardation in association with behavior problems in older children often make for even more complicated and difficult decisions in which the advice of the family physician may be relied upon heavily.

Few physicians are likely to have the time to remain familiar with all developments in the field of mental retardation or to organize personally a total evaluation and treatment program for their mentally retarded patients. Available to the physician, however, are the assistance of the county welfare departments, community mental health centers, the staffs of the nearest institution for the mentally retarded, the local public health nurse, the resources of the State Department of Public Welfare, and the resources both state and local of the Associations for Retarded Children. The latter organizations contain many parents who may be particularly helpful because they have successfully faced the problems associated with having mentally retarded children.

This article is intended primarily to alert the physicians of Minnesota to these Departments of Public Welfare policies and underlying philosophy. Questions which these policies raise that are not answered in the article should be directed to the Medical Services Division of the Department of Public Welfare, where they will be welcomed and responded to immediately.

Richard E. Bartman, M.D.**
St. Paul, Minnesota

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*This is very thoroughly discussed in a publication of the Group for the Advancement of Psychiatry titled, *Mental Retardation: A Family Crisis — The Therapeutic Role of the Physician.* Copies of this report can be obtained for 50¢ from: Publications Office, Group for the Advancement of Psychiatry, 104 East 25th St., New York, N. Y., 10010. Another helpful publication is *Mental Retardation: A Handbook for the Primary Physician* issued by the American Medical Association. Copies can be obtained for 40¢ from: American Medical Association, 535 North Dearborn Street, Chicago, Illinois, 60610.

**Director, Childrens Mental Health Services, Medical Services Division, Department of Public Welfare, State of Minnesota.

Ours is an age which is proud of machines that think, and suspicious of any man who tries to. — Howard Mumford Jones

Photographic Contest

The Editors of MINNESOTA MEDICINE, in collaboration with the Doctors' Photographic Society of Minneapolis, take pleasure in announcing a monthly photographic contest. The contest is to promote an interest in photography in the medical profession. First prize each month will be publication in full color of the winning picture in MINNESOTA MEDICINE.

The following rules will govern the conduct of the contest:

1. Only doctors of medicine are eligible to submit pictures, and the picture must have been taken or composed by a physician.
2. Each contestant may submit not more than two pictures each month.
3. Only color transparencies, 35 mm. to 2¼", can be considered.
4. Each slide should be labeled with the maker's name, address, and the identifying title.
5. Slides should not be mounted on glass, but can be protected in plastic sleeves or envelopes.
6. Each entry must be accompanied by a self-addressed, stamped envelope if return of the picture is desired. Returns will be made shortly after the close of the contest each month. The winning photograph will be retained but will be returned after it has been used.
7. The deadline date for entry will be the 10th of each month and the winner of each month's contest will be announced in MINNESOTA MEDICINE in the subsequent issue. The date of publication will be three to six months in advance.
8. There will be no limitation on subject material except as indicated in item 10.
9. Model releases will be requested of winners where appropriate.
10. Judges will be selected by the editors of MINNESOTA MEDICINE and the Doctors' Photographic Society. The judges will be guided by the precepts of the Photographic Society of America, and winners will be based on appropriateness, interest, impact, and technical excellence.
11. The editors of MINNESOTA MEDICINE and the Doctors' Photographic Society cannot be responsible for entries lost or damaged, but every effort will be made to protect submitted pictures.

Your pictures are hereby invited. Please submit pictures to:

Photo Contest Editor
MINNESOTA MEDICINE

Announcing

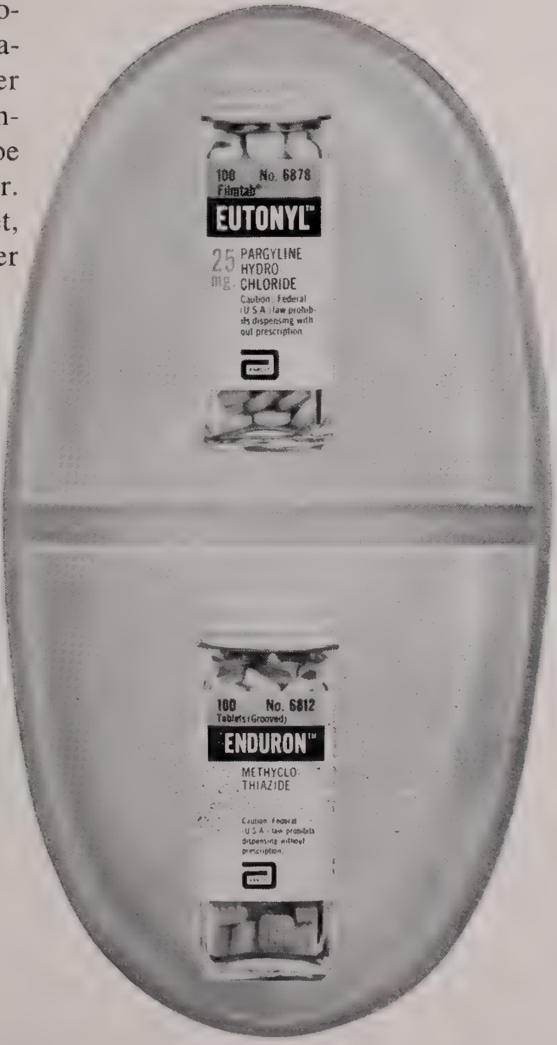
EUTRON™

pargyline hydrochloride 25 mg. and methyclothiazide 5 mg.

for control of
moderate to severe
hypertension

Unique combination produces greater antihypertensive effect with lower doses

Eutron is the combination in a single tablet of 25 mg. Eutonyl (pargyline hydrochloride) and 5 mg. Enduron (methyclothiazide). This combination produces greater therapeutic effect than that of either component used alone. Side effects may be milder, too, as dosages are generally lower. The effective dosage is usually one tablet, once daily. Tablets are scored for greater dosage flexibility.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Each Eutron tablet contains two proven antihypertensives in the ratio shown to be most effective in most patients.

TM—TRADEMARK

New **EUTRON** extends your range of treatment in moderate to severe hypertension

A single product you can use even in the presence of congestive heart failure or edema

Eight out of 10 patients respond

In clinical trials, Eutron produced normotension or a significant reduction in blood pressure in eight out of 10 patients studied. The rationale for the product is this: Eutonyl used alone is a potent antihypertensive. Its antihypertensive action is markedly enhanced by Enduron, a potassium-sparing thiazide.[1,2,3] The combination (Eutron) thus produces greater antihypertensive effect with lower dosages of the Eutonyl component, and milder side effects may be seen.

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1. Torosdag, S., Schvartz, N., Fletcher, L., Fertig, H., Schwartz, M. S., Quan, R. F. B., and Bryant, J. M., Pargyline Hydrochloride as an Antihypertensive Agent With and Without A Thiazide, Am. J. Cardiol., 12:822, Dec., 1963.

2. Pollack, P. J., Pargyline Hydrochloride and Methyclothiazide Combined In The Treatment of Hypertension, Cur. Thera. Res., 7:10, Jan., 1965.

3. Bryant, J. M. et al., Antihypertensive Properties of Pargyline Hydrochloride, New Non-Hydrazine Monoamine Oxidase Inhibitor Compared with Sulphonamide Diuretics, J.A.M.A., 178; 406, Oct., 1961.

BP reductions in the recumbent and sitting positions often are nearly as great as in the standing. In clinical trials, the average *recumbent* BP reduction was 36/18 mm. Hg.

The average *standing* reduction in clinical trials was 45/22 mm. Hg. Thus the difference between the standing and recumbent readings was only 9/4 mm. Hg.

Significantly lowers blood pressure in all body positions; less likelihood of orthostatic hypotension

In clinical trials, the average reduction in standing blood pressure was 45/22 mm. Hg.; in the sitting position it was 48/20 mm. Hg.; and in the recumbent position, 36/18 mm. Hg.

Because Eutron effectively reduces blood pressure in all body positions, there is reduced likelihood of orthostatic symptoms or hypotension.

This was reflected in the relatively mild character of side effects seen in clinical trials (see below).

Smooth and gradual onset

Onset of antihypertensive action is usually quite smooth. Initial reduction of systolic and diastolic readings is usually seen within a week – maximum reduction in seven to ten days.

Less troublesome side effects may be seen; frequent improvement in "sense of well-being"

Fewer than 1% of patients studied discontinued Eutron therapy because of side effects. This is due in part to the relatively low dosage needed with the combination. Usual recommended dose is one tablet daily—that is, 25 mg. Eutonyl with 5 mg. Enduron. *This is about half the usual therapeutic dose of Eutonyl given alone.* As a consequence side effects may be milder. And, as with Eutonyl given alone, the patient may well note an increased sense of well being. This is in distinct contrast to most other antihypertensive therapy.

ABBOTT

Prescribing information for **EUTRON**

INDICATIONS: Eutron (pargyline hydrochloride and methyclothiazide) is indicated in the treatment of patients with moderate to severe hypertension, especially those with severe diastolic hypertension. It is not recommended for use in patients with mild or labile hypertension amenable to therapy with sedatives and/or thiazide diuretics alone.

CONTRAINDICATIONS: Eutron is contraindicated in patients with pheochromocytoma, advanced renal disease, paranoid schizophrenia and hyperthyroidism. Until further experience is gained it cannot be recommended for use in patients with malignant hypertension, children (under 12 years of age), or pregnant patients.

The concomitant use of the following is contraindicated: other monoamine oxidase inhibitors; parenteral forms of reserpine or guanethidine; sympathomimetic drugs; foods high in tyramine such as cheese; imipramine and amitriptyline, or similar antidepressants; methyldopa. A drug-free interval of two weeks should separate therapy and use of these agents.

WARNINGS: Pargyline hydrochloride is a monoamine oxidase inhibitor. Patients should be warned against eating cheese, and using alcohol, proprietary drugs or other medication without the knowledge of the physician. When it is necessary to administer alcohol, narcotics (notably meperidine), antihistamines, anesthetics, barbiturates and other hypnotics, sedatives, tranquilizers, or caffeine, these agents can be used cautiously at a dosage of ¼ to ⅕ the usual amount. Avoid parenteral administration where possible. Withdraw pargyline two weeks before elective surgery.

Patients should be warned about the possibility of postural orthostatic hypotension. Those with angina or other evidence of coronary disease should not increase physical activity. Pargyline may lower blood sugar. Potassium depletion is unlikely at the recommended dosage, but if it occurs, adjust dosage or withdraw or provide added natural food sources of potassium; potassium tablets should be avoided wherever possible, as bleeding or obstructive ulceration of the small bowel has been associated with their use; potassium levels should be especially watched if the patient is on digitalis or steroids, or if hepatic coma is impending.

PRECAUTIONS: When determining the antihypertensive effect of Eutron, blood pressure should be measured while the patient is *standing*. Use with caution in hyperactive or hyperexcitable persons. Such persons may show increased restlessness and agitation. Withdraw drug during acute febrile illness. Watch patients with impaired renal function for increasing drug effects or elevation of BUN and other evidence of progressive renal failure; withdraw drug if such alterations persist and progress. Pargyline has not been shown to cause damage to body organs or systems. As with all new drugs, complete blood counts, urinalyses, and liver function tests should be performed periodically. The drug should be used with caution in patients with liver dysfunction. With prolonged therapy, examine patients for change in color perception, visual fields, and fundi.

Elevated blood urea nitrogen, serum uric acid or blood sugar are possibilities attributable to the methyclothiazide in Eutron. Methyclothiazide may also reduce arterial response to pressor amines. Blood dyscrasias, including thrombocytopemia with purpura, agranulocytosis and aplastic anemia, have been seen with thiazide drugs.

SIDE EFFECTS: The use of pargyline may be associated with orthostatic hypotension. Mild constipation, slight edema, dry mouth, sweating, increased appetite, arthralgia, nausea and vomiting, headache, insomnia, difficulty in micturition, nightmares, impotence, delayed ejaculation, rash, and purpura have been encountered with pargyline. Hyperexcitability, increased neuromuscular activity (muscle twitching) and other extra-pyramidal symptoms have been reported. Drug fever is extremely rare. Congestive heart failure has been reported in a few patients with reduced cardiac reserve. Nocturia has been observed with the combination. If side effects persist, despite symptomatic therapy or reduction of the dose, discontinue the drug.

ABBOTT

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Clinical Path Conference

Quadriplegia in a Patient on Anticoagulant Therapy

A 51-year-old married white male engineer was admitted to St. Barnabas Hospital on September 12, 1964, with a four-day history of intermittent chest pain. The pain was more severe with each attack, radiating to the back and both shoulders, and was accompanied by nausea and vomiting. In 1956, he had a myocardial infarction, and in December, 1962, he suffered a second infarction. He was placed on bisoxycoumarin (dicumarol) therapy, which was continued until his final admission. A duodenal ulcer was first demonstrated in 1957 and was seen again on x-ray during his 1962 admission. His gallbladder had been removed in 1944.

Physical Findings

He was obese and apprehensive but not dyspneic. The blood pressure was 130/80, the pulse 94 and regular, and the temperature 99°F. The neck veins were not engorged. Heart tones were good with a normal rate and rhythm. The chest was clear; no rales or abnormal breath sounds were heard. A healed scar was present below the right costal margin. The liver and spleen were not palpable. No peripheral edema was observed. The admitting diagnosis was coronary insufficiency with impending myocardial infarction.

Laboratory Studies

The admission laboratory work included a hemoglobin of 14.7 gm.% and a white blood cell count of 12,000 with 80 polymorphonuclear leucocytes and 12 band forms. The urinalysis showed a pH of 6.5, a specific gravity of 1.017, and 40-50 red cells per high-power field. A prothrombin time on September 14 was 39 seconds (control 12.2 seconds) and on September 15, 25 seconds (control 12.9 seconds). The serum glutamic transaminase for the first three days of hospitalization was 28 units, 49 units, and 56 units (normal 4-40 units). Electrocardiographic changes indicated a healed anterior myocardial infarction. The chest x-ray was normal.

Progression of Symptoms

On the second day the patient experienced muscle pain in the neck and shoulder, which increased with movement. The muscles were tender to palpation. Ecchymoses of the skin were observed. On the fourth day he suddenly developed generalized weakness and was unable to move his legs or lift his arms. Neurological examination disclosed diffuse tenderness over the posterior neck and shoulder, a right sixth nerve paresis, extreme weakness of the sternocleidomastoid, deltoid, and triceps muscles, total flaccid paraplegia, areflexia, and bilateral absence of pain, temperature, and touch below C-5. The intercostal muscles barely moved. His breathing was diaphragmatic. Cough and swallowing were poor.

On September 16 a lumbar puncture was done. The opening pressure was 120 mm. of water, and the fluid showed a protein of 4680 mg./100 ml., 14,750 RBCs/mm.^{3}, and 81 WBCs/mm.^{3}. A tracheostomy was performed. Laboratory studies completed the following morning included a hemoglobin of 12.0 gm.%, a WBC of 10,200/mm.^{3}, normal blood urea nitrogen and serum electrolytes, and a prothrombin time of 14.5 seconds (control 12.7 seconds).

Late in the afternoon of September 17, he complained of excruciating pain in the posterior neck. A lumbar puncture was repeated; the Queckenstedt maneuver was

Continued

normal; a myelogram was performed. Later that evening, the patient was taken to the operating room where an emergency cervical laminectomy was performed.

Lawrence Farber, M.D.:*

The case for today is a 51-year-old married white male engineer with a four-day history of intermittent chest pain, accompanied by nausea and vomiting. Eight and two years previously he had a well documented myocardial infarction. He was placed on dicumarol therapy after the second episode. He has a seven-year history of a duodenal ulcer.

The History

Let us consider the history — the most important part of diagnosis in medicine. We have an individual with two preceding myocardial infarctions, and I assume that chest discomfort had been present. He complains of intermittent chest pain, radiating into the back and both shoulders. The pain is associated with nausea and vomiting, a common occurrence with myocardial infarction.

It is known that he had a duodenal ulcer. With pain radiating into the back and between the shoulder blades, and even chest pain, a perforating ulcer must be considered. Other considerations are pulmonary emboli, infectious processes, dissecting abdominal aneurysm of the aorta, acute pancreatitis, and liver disease.

The Physical Examination

With a blood pressure of 130/80, a pulse of 94, a clear chest, and no engorged neck veins, an extensive myocardial infarction is unlikely. No evidence of severe myocardial failure exists, though impending myocardial infarction is possible.

The admission white blood cell count was 12,000 with 80 polys and 12 band forms. The urine showed 50 red cells per high-powered field, probably resulting from anticoagulants, though the prothrombin time on September 14 was only 39 seconds (control 12.2 seconds). On September 25 the prothrombin time was 25 seconds (control 12.9 seconds). Three days after admission, his prothrombin time was still very high. What his prothrombin times were on the outside and whether these determinations represented a recent rise in the prothrombin time are not known. The electrocardiogram revealed a healed anterior myocardial infarction; there were no acute changes.

Course in Hospital

On the second day he had pain and tenderness of the muscles of the neck and shoulder. Ecchymoses of the skin were observed. On the fourth day he suddenly developed generalized weakness and was unable to move his legs or lift his arms. Four days after his admission he developed quadraparesis. Neurological examination disclosed diffuse tenderness over the posterior neck and the shoulders, a right sixth nerve paresis, extreme weakness of the sternocleidomastoid, the deltoid, and triceps muscles, a flaccid paraplegia, areflexia, and absence of the intercostal respiration.

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*Attending Neurologist, St. Barnabas Hospital.

Differential Diagnosis

Mid-Cervical Lesion

He was evidently breathing with his diaphragm which receives innervation from C3, C4, and C5, as we know that his intercostal muscles, which are thoracically innervated, were out. His triceps muscles, which derive their innervation from the seventh and eighth cervical nerve roots, were very weak. The deltoid muscles, which receive innervation from the fifth and sixth nerve roots, were also weak. The biceps muscles were not mentioned. The sensory level is about C5. The lesion, whatever it is, is in the mid and lower cervical region. The severe weakness of the sternocleidomastoid muscles suggests derangement of the eleventh cranial nerve, the third cervical nerve, and possibly the fourth. The difficulty with swallowing and cough suggests vagus nerve involvement. A right sixth cranial nerve paresis is present.

Extensive Cord Involvement

We have extensive spinal cord involvement; in addition, we have patchy lower cranial nerve involvement and muscle tenderness and pain. I see nothing about radicular pain radiating down the arms or legs.

On September 16, a lumbar puncture revealed the pressure to be 120 mm. of water — a normal pressure. The fluid showed a protein of 4,680 mg., 14,750 RBC and 81 WBC. This is indeed a very, very high spinal fluid protein. Froin's syndrome* — resulting from a total or partial spinal column block — is the only condition reported with proteins of four, five, and six grams.

An emergency tracheostomy was performed because of further respiratory difficulty, to provide more effective pulmonary toilet and to facilitate the use of the Bird or Bennett Respirators.

Laboratory studies completed the following morning revealed a prothrombin time of 14.5 seconds and a control of 12.7 seconds. This is within the normal range. Late in the afternoon on September 17, five days after admission, he complained of excruciating pain in the posterior neck. A spinal tap was repeated; the Queckenstedt maneuver was normal; a myelogram was performed.

Lesions Causing Cord Transection

Few things will cause such an acute process to develop. Because of the severe but focal neurological signs, one has to consider local lesions causing spinal cord transection. Excessive anticoagulation must be considered. Hematomyelia (bleeding into the spinal cord) or intradural or epidural hematoma may have caused acute, severe spinal cord compression and a transection syndrome. Expansion of a tumor of the lower cervical cord enters into the diagnosis. A person on anticoagulants could have hemorrhaged into a metastatic neoplasm or a primary tumor of the spinal cord. A vertebral body with metastatic tumor or extensive osteoporosis could have collapsed to cause the cord compression.

Guillain-Barre Syndrome

In addition to the cord lesion, the sixth, tenth, and twelfth cranial nerves were involved. Polyneuritis can come on acutely. The cardinal signs and

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*See Page 152.

Continued

symptoms of Guillain-Barre syndrome include muscle tenderness and radicular pain. Its course can be either acute or chronic. Recently we saw a 16-year-old girl who developed a quadriplegia and total loss of respiratory ability within three or four hours. Besides peripheral nerve involvement, there may be deep muscle tenderness and radicular pain, weakness, numbness; the spinal cord, cranial nerves, and at times even the brain can be affected. A polyneuropathy in the presence of a bleeding tendency is, of course, possible.

The exceedingly high spinal fluid protein — almost 5 grams/100 ml. — probably eliminates polyneuritis as the primary process. The high protein is more likely in the partial or total block. The Queckenstedt was negative, but this is not significant, as even a pin-sized hole can provide a normal variance in pressure during the Queckenstedt maneuver. I assume this high protein results from the partial or almost total spinal fluid block. Perhaps the radiologist can tell us more about the nature of the block.

Dr. Philip Olson*

A cervical myelogram performed on September 17 revealed a complete block to the flow of panopaque at the level of the disc space between C6-C7. A trickle of panopaque is attempting to go along the right lateral aspect of the lower cervical spine. It should be immediately adjacent to the bone, but here it is elevated. This would indicate a space-occupying lesion in the lower cervical area, located anteriorly and displacing the column posteriorly.

Dr. Lawrence Farber

Does this look like intramedullary or extramedullary bleeding?

Dr. Philip Olson

Since the panopaque is displaced posteriorly, an extradural lesion is more likely. It could be interpreted as intramedullary on the basis of the posteroanterior films, but the lateral film indicates an extradural location.

Dr. Lawrence Farber

Now we know the lesion is probably extradural. A hemorrhagic process seems to be the most logical diagnosis. It would be foolish to ignore the high prothrombin time in the face of blood in the urine and in the skin. Bleeding may be the reason for the compression of the spinal cord. Therefore, we may be dealing here with an extradural hematoma anterior to the spinal cord causing a transection syndrome in the lower cervical area with a clinical quadriplegia. It is difficult to explain the cranial nerve involvement, particularly the tenth, eleventh, and right sixth nerves, except on the basis that more extensive hemorrhage has taken place. Brain stem hemorrhages could account for the dysphagia, particularly with hemorrhages in and around the nucleus ambiguous. Other entities such as tumor with hemorrhage must be considered. An infectious process is not likely.

Dr. Lawrence Farber's Diagnoses:

1. Epidural hemorrhage of cervical spinal cord secondary to dicumarol

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*Radiologist, St. Barnabas Hospital.

therapy.

2. Focal hemorrhage into brain with involvement of sixth, tenth, and eleventh cranial nerves.
3. Coronary sclerosis with old myocardial infarction.

Dr. Donald Mac Kinnon

I believe anticoagulant bleeding may be the answer. Strange complications can occur. About ten days ago we saw a lady with an acute abdomen. She was thought to have an appendicitis. She gave a history of taking birth-control pills for several years and had a recent thrombophlebitis of the leg five weeks before I saw her. She was put on dicumarol for the thrombophlebitis and was in the hospital for about ten days. She had recently had a prothrombin time in the therapeutic range, but a repeat prothrombin time revealed 71 seconds. She was given Mephyton. The next day her abdominal symptoms and signs had disappeared. We cannot substantiate dicumarol bleeding, but it is a plausible explanation for her symptoms and course. Two drugs may have caused her malady: the birth-control pills and the dicumarol.

Dr. Carl O. Rice

The usual complications occurring with dicumarol are ecchymoses, bleeding from the kidney, and hematuria; but it is the unusual ones that disturb us. A year ago I had a patient with an acute abdomen. Distention and melena without massive hemorrhage were observed for a few days without any improvement in the symptoms. She had been on dicumarol, and the prothrombin time was about 29 seconds (normal 14). The bleeding symptoms persisted despite repeated tranfusions.

At exploration we found the mesentery of the entire gut swollen and edematous, with patches of ecchymosis scattered throughout. In the wall of the gut we saw intramural hemorrhage; within the lumen of the gut we saw larger patches of melena. Subsequently she was given Vitamin K and made a satisfactory recovery.

The coagulation scheme is complex and spontaneous bleeding can occur if a deficiency exists in any of the coagulation stages or with an excess of anticoagulant. The prothrombin time can be altered by fever, salicylates, liver disease, or a number of other conditions. The muscle tenderness which was observed could be due to extravasation of blood into the muscles.

In this patient, Dr. Farber, the operation was indicated because of the nature of the cord transection and the possibility of relieving the compression. I would expect on the basis of the cranial nerve findings that there were additional hemorrhages higher, in the brain stem.

Dr. Lawrence Farber

Complications of anticoagulant therapy occur in all realms of neurology. Subarachnoid or epidural hemorrhage occasionally happens. Intracerebral hemorrhages in the area of the basal ganglia or temporal lobe are frequently reported, occurring most often in association with straining and heavy lifting. Anticoagulants can be a two-edged sword and in this patient the hemorrhage was catastrophic, resulting in over-anticoagulation. The high protein concentration in the spinal fluid, in spinal block, almost as

Continued

high as in the blood stream, is not thoroughly understood. Stagnation occurs. Much of the protein, particularly if it is in the presence of a tumor, would come from the surrounding tissue itself. Water is drawn out; protein is not. These physiologic mechanisms create the elevated protein.

Dr. Richard Reece

As a rule, for every 1,000 RBC there is a 3 mgm. rise in protein. With 15,000 red cells, a rise of 45 mg. per 100 ml. would result. This falls far short of the 4750 mg. elevation in this patient.

Dr. Lyle Hay*

The protein elevation of the spinal fluid is due to extradural hemorrhage which in turn caused the block. It is not merely the presence of blood in the spinal canal.

Pathological Discussion

Dr. Richard Reece**

I omitted this patient's course after laminectomy in order to concentrate on the nervous system. After the laminectomy, the dura was left open for decompression. One day later he developed a distended abdomen, was operated on, and a perforated ulcer was found. He died shortly after operation. At autopsy the principal gross findings were a large organized anterior epidural hematoma and diffuse peritonitis.

Dr. J. Popowich

We removed the cord from the posterior approach. The hematoma extended from the third cervical vertebra to the lumbar area. The cervical cord was compressed and flattened. Microscopically, extensive degeneration and necrosis were observed in the anterior cord adjacent to the hematoma. In Guillain-Barre disease the changes usually occur in the posterior columns and sometimes are associated with demyelinization and chronic inflammation around the dorsal root.

Dr. Richard Reece

There was no other hemorrhage within the body. In the brain, I saw focal encephalomalacia, a change which, I suppose, could be secondary to a polyneuritis. Guillain-Barre syndrome is hard to document in its acute stages. At two days, only edema is seen; at one week, necrosis and degeneration, and at nine days, perivascular lymphocytic reaction around the dorsal roots. After looking at all the slides, I cannot make the diagnosis or exclude it. Other findings included an old anterior myocardial infarction with a sclerosis of his anterior descending coronary artery. He had diffuse peritonitis from the perforated ulcer.

The Dilemma

Spurney and his group in Kansas City reported two cases of epidural hematomas with anticoagulants and found eight in the literature.[1] Thirty-five patients with spontaneous hemorrhage had not received anticoagulant

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*Director of Medical Education, St. Barnabas and Swedish Hospitals.
**Pathologist, St. Barnabas Hospital.

therapy. Eight of the ten patients on anticoagulants had prothrombin times within the normal therapeutic range.

There are fifteen reported cases of "spontaneous" subdural hematomas. In eight the prothrombin times were in the normal range.[2] Even if the clinician treats the patient appropriately and the prothrombin times are within the therapeutic range, the patient still may bleed. Despite this dilemma it is the general feeling that the good aspects of anticoagulant therapy outweigh the bad. An unquestioned benefit occurs with treatment of thrombophlebitis. However, there is some controversy about anticoagulant therapy in people with coronary artery disease.[3] In general, prophylactic anticoagulation has been abandoned for cerebrovascular sclerosis or thrombosis.

Bleeding in the Therapeutic Range

Why do patients bleed in the therapeutic range? Many are subsequently proven to have an underlying disease.[4] This is particularly true in the gastrointestinal tract. Bleeding in the normal range should initiate a search for an organic lesion.

Owren of Scandanavia states that the Quick prothrombin time is not sensitive enough to detect the Factor X.[5] He claims that the use of thromboplastins insensitive to Factor X are the most frequent cause of bleeding during anticoagulant therapy. He developed a test, Thrombotest, with a high sensitivity to Factor X.[6] Another problem confronting the clinician is the difference between laboratories as to how prothrombin times are reported — per cent, ratios, and seconds — with resulting confusion.[7]

Bizarre Complications with Anticoagulants

The lesson here is to look for bizarre complications in a patient on anticoagulants. One is *adrenal hemorrhage* with acute adrenal insufficiency. These patients experience nonspecific abdominal pain, ileus, and high fever. This complication is usually unrecognized. Fourteen cases have been reported.[8] A second complication is a rapidly enlarging *pericardial effusion*.[9] These patients did not have myocardial infarcts, but still bled into the pericardial cavity. Other complications are *necrosis of the skin, gangrene of the breasts, hemorrhagic pancreatitis,* and a curious lesion known as the *"Purple Toe Syndrome."*[10-13] There was a recent case report of *hemorrhage into a pituitary adenoma,* with deiplopia and subsequent death.[14] As Doctors Rice and MacKinnon have mentioned, there have also been reports of small and large bowel obstruction, secondary to bleeding into the intestinal wall.[15,16]

I have performed an autopsy on a man who went blind during a bowel movement. He was on long term anticoagulation therapy. His prothrombin time was 34 seconds. He had a "spontaneous" subdural hemorrhage at necropsy.

Probably the most tragic cases are *fatal hemorrhage in infants* whose mothers are on anticoagulants.[17]

Strange complications can occur in patients on anticoagulation therapy. I sympathize with the clinicians. They are on a fulcrum; on the one side they face the deadly threat of thrombosis and on the other the ominous consequences of hemorrhage. We can never fully realize the potentialities of the drugs we use. In New Haven it was found that 20 per cent of

Continued

hospitalized patients suffered adverse effects from diagnostic and therapeutic agents or procedures.[19] Bleeding as a complication of anticoagulant therapy occurs in about 10 per cent of hospitalized patients and in about 40 per cent of ambulatory patients.[18] We can standardize drugs and perfect techniques, but we cannot standardize people.

Dr. Lawrence Farber

Epidural hematomas of the spinal cord occur in other situations than in the presence of anticoagulation therapy. In the last three years we have had two instances of epidural hematoma occurring within a day of laminectomy. Fortunately these were found in time and decompressed. A most curious case was that of a man with a past history of tuberculosis and diabetes who had a transection syndrome three weeks after a whiplash injury. He had not been on anticoagulants but at operation was found to have a spontaneous epidural hematoma. This could have been secondary to vascular malformations of the vertebral body or to the preceding trauma.

Anatomical Diagnosis

1. *Organizing anterior epidural hematoma (probably secondary to dicumarol therapy) with degeneration and necrosis of anterior portion of the spinal cord.*
2. *Duodenal ulcer with rupture and diffuse peritonitis.*
3. *Severe coronary artery sclerosis with old myocardial infarction.*
4. *Focal encephalomalacia of the brain.*

St. Barnabas Hospital
Minneapolis, Minnesota

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4-19 May be secured from the author or the reprints.

FROIN'S SYNDROME

The massive coagulation-xanthochromic syndrome originally described by Froin refers to an increased amount of exudative products found in the spinal fluid below the level of a partial or complete block of the spinal canal. The high protein level of the spinal fluid has been attributed to spinal cord tumor. There is a flaccid or spastic paraplesia, sensory and sphincter disturbances, and in some instances subjective pain is evident. The neurologic disturbances depend upon the level of the block, which usually is observed in the lumbar region.

The spinal fluid undergoes spontaneous coagulation and is found to contain a large amount of globulin with a high total of protein. Xanthocromia is evident and there is a decrease in spinal fluid pressure with no elevation on coughing.

This condition is found in secondary neoplasms, Pott's disease, Landry's paralysis, serous or tuberculous meningitis, meningomyelitis, and pachymeningitis.

If the underlying pathology is benign, laminectomy and decompression may afford favorable prognosis.

Durham, Robert H. — Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

Grand Rounds

Traumatic Aortic Aneurysm

When an individual sustains thoracic injury of such a magnitude as to tear the aorta, the consequence is generally immediate death from hemorrhage.[1] However, the aortic rupture may be confined to a hematoma within the mediastinum, and the diagnosis of traumatic aneurysm of the thoracic aorta may be made some time later.[2] After such a post-traumatic aneurysm has been detected, the patient should be evaluated for operative repair.

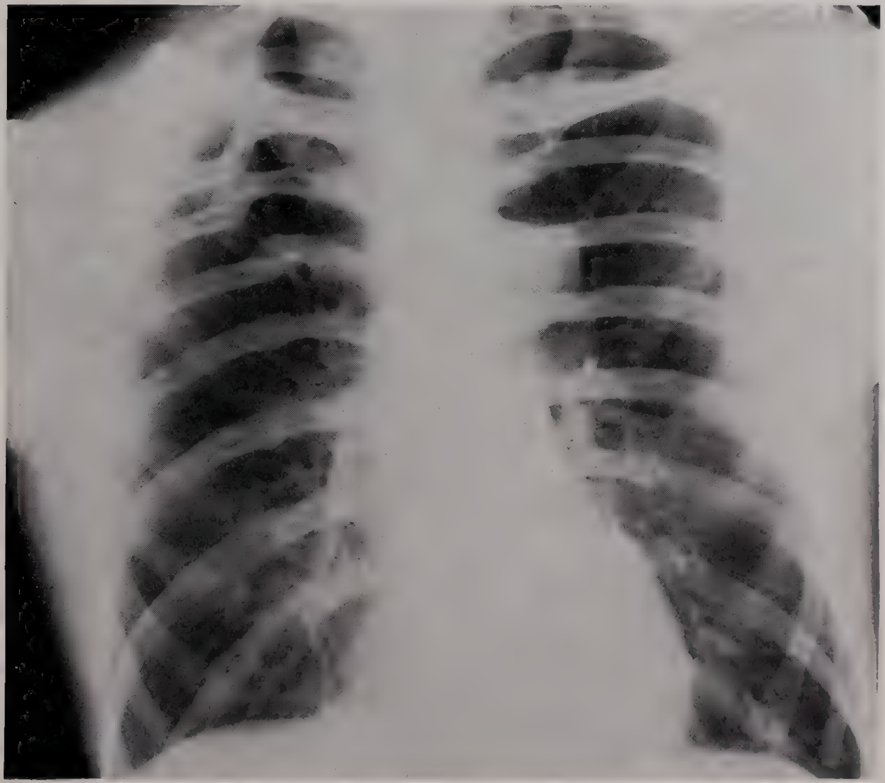


Fig. 1 — Routine chest x-ray (Case 1).

Continued

Case Report

A twenty-nine-year-old white male was admitted to the Dearborn Veterans Hospital on April 17, 1964, with lower back pain resulting from an automobile accident that occurred November 11, 1963. While making a left turn, his car was struck by two other automobiles, pinning him between the steering wheel and the front seat. He was immediately hospitalized and found to have a fractured right clavicle, multiple rib fractures, fracture of the lumbar vertebra, a right hemopneumothorax, a laceration of the right lobe of the liver, and rupture of the right kidney.

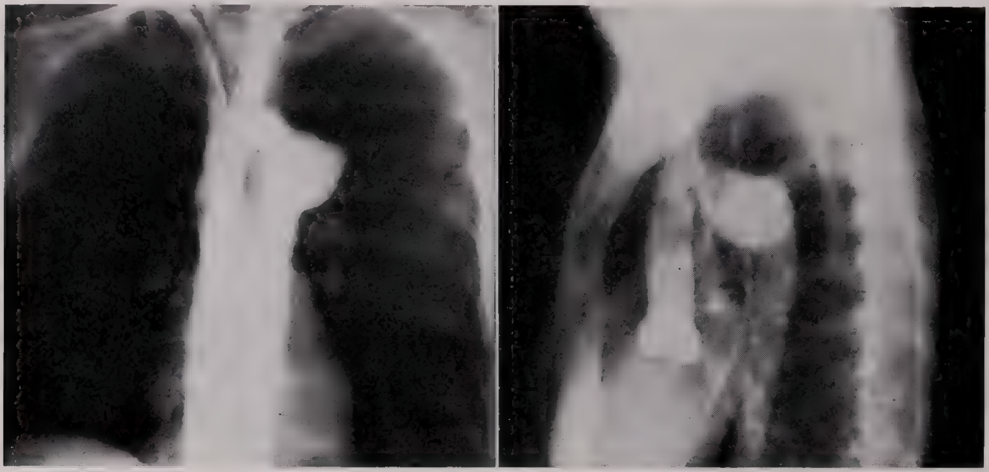
Shortly after admission he underwent right nephrectomy and repair of the liver injury. Postoperatively, because of renal failure, dialysis was required. After renal function returned and the fractured clavicle had been repaired, the patient was eventually discharged in March 1964. When seen at our hospital, he denied cardiorespiratory symptoms. His past history was not contributory.

Physical Examination

Physical examination revealed the blood pressure to be 110/80 mm. Hg. in both arms and 130/100 in both legs. The pulse was regular and no heart murmurs were present. There was a deformity of the right clavicle. Minimal tenderness was present over the lower lumbar vertebrae, but there were no reflex, motor or sensory changes in the lower extremities. The electrocardiogram was normal and the laboratory work otherwise noncontributory.

X-ray Findings

X-rays of the lumbosacral spine showed post-traumatic changes of the fifth lumbar vertebra. The chest x-ray was interpreted as showing, in addition to healed fractures of the right third through tenth ribs posteriorly, an unusual expansion of the aortic knob (Figure 1). A retrograde aortogram demonstrated a saccular aneurysm, 5 cm. in greatest diameter, arising in the descending aorta 3 cm. distal to the subclavian artery (Figures 2a and 2b).



Figs. 2 (a-left) and (b-right) — Retrograde aortogram (Case 1).

Operation

No specific treatment was recommended for the patient's back. Surgical treatment of the aneurysm was decided upon and accomplished on June 3, 1964. The right brachial artery pressure was monitored. The left chest was entered through the bed of the fourth rib. A 4 x 6 cm. aneurysm of the descending aorta was separated from adherent lung, pulmonary artery, and esophagus. Blood was shunted from the left atrium to the left femoral artery at a rate of 1200 cc./min. during a 30-minute period while the aorta was occluded proximal to the origin of the left subclavian artery and again distal to the aneurysm. After the aneurysm had been entered, it became apparent that the aortic wall had been torn transversely for about ¾ of its circumference (Figure 3). A two-inch segment of aorta containing the aneurysm was resected and replaced with a Teflon graft. The postoperative course was uneventful and the patient was discharged on the twenty-first postoperative day (Figure 4). He remains well and has returned to normal activity.

Discussion

Symptoms

Many patients with chronic aortic aneurysms after trauma have no

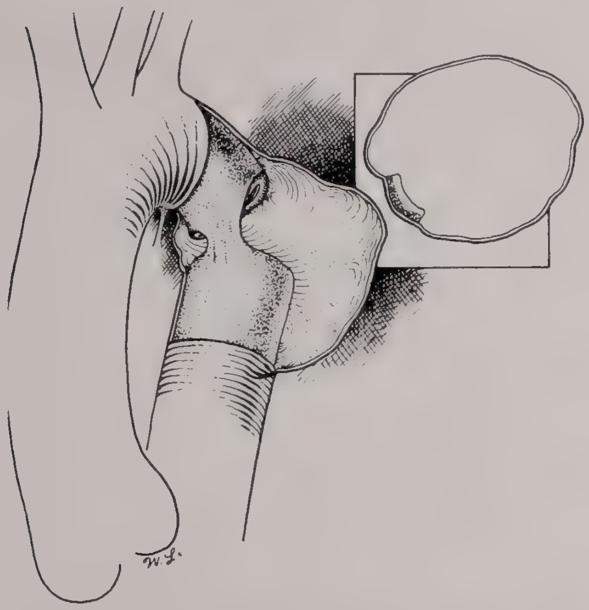


Fig. 3 — Diagram of traumatic aneurysm demonstrating that a portion of aortic wall was intact.

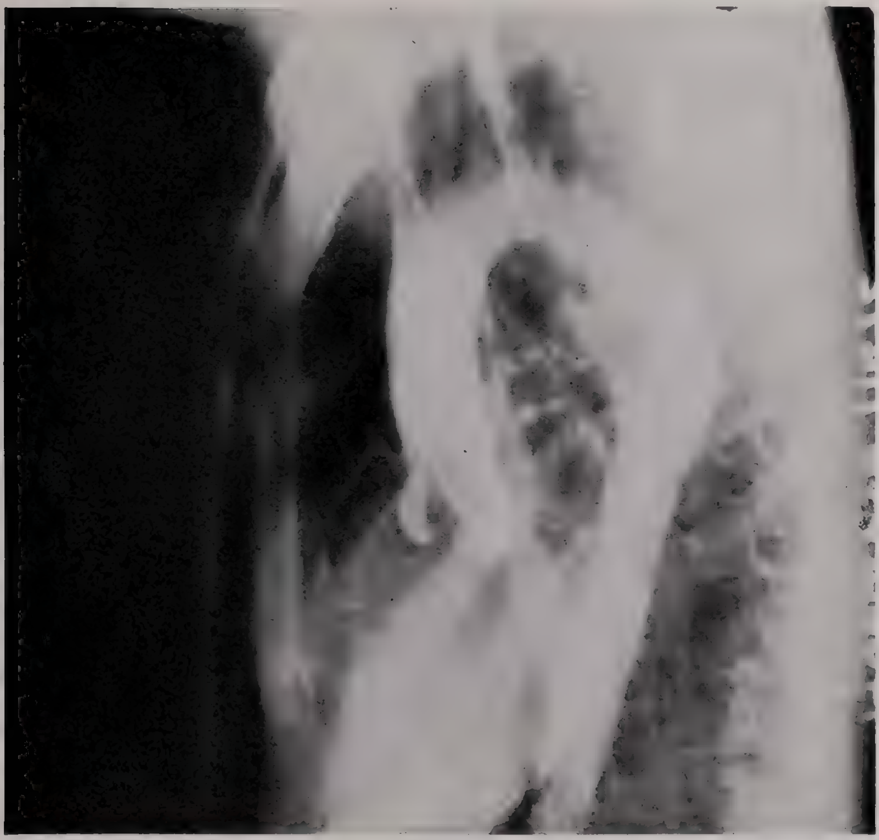


Fig. 4 — Aortogram after aortic aneurysm resection and replacement with Teflon prosthesis.

Continued

symptoms but present with abnormal chest x-ray and the history of injury.[3]

Symptoms when present are related to blood loss, a space-occupying mass, dissection or infection. The blood loss is visible if the aneurysm ruptures into the bronchus or esophagus. The rupture of an aneurysm is usually progressive, and signs and symptoms usually occur prior to total exsanguination. An expanding aneurysm, if contained within the mediastinum, is usually associated with pain. The first bleeding episode generally stops, only to recur again to a greater degree within hours. Dysphagia, dyspnea, cough and hoarseness are symptoms of an aneurysmal mass exerting pressure on the esophagus, bronchus or recurrent nerve. The symptoms of heart failure and sepsis are related to aneurysm dissection and infection and only rarely found.

Diagnosis

A high index of suspicion is most important in diagnosis. Shonholtz[4] et al. emphasized that the orthopedic surgeon sees many of these patients first because of multiple injuries. Every steering-wheel accident or severe chest-wall impact ought to have a careful x-ray evaluation of the mediastinum. Wyman[5] in 1953 called attention to the clues relating to aortic trauma, that include mediastinal widening, aortic arch dislocation, and aortic arch indistinctness. Steinberg[3] has found that fluid in the left chest associated with a localized bulge adjacent to and indistinguishable from the aortic knob is suggestive of aneurysm. Emergency forward venous aortograms can be done readily, even on the seriously ill, by injecting contrast material into the right atrium and taking films based on the circulation time.[6] The more chronic aneurysms can be better visualized by retrograde arterial study.

Treatment

After Blalock[7] first successfully treated a thoracic aneurysm related to penetrating trauma, it was speculated that aneurysms relating to blunt trauma could be similarly managed surgically. Bahnson[8] was the first to resect an aneurysm and repair an aorta. If the aortic repair was such that there was inadequate approximation of normal aortic wall, recurrence was noted. DeBakey and Cooley[9] first resected a traumatic thoracic aneurysm that was recurrent. Hypothermia was used to permit aortic occlusion and a homograft employed to establish aortic continuity. Teflon and dacron prostheses are now thought to be superior to a homograft. Alley[10] has pointed out that there usually is no loss of adjacent normal artery. It is, therefore, sometimes possible to do a direct anastomosis of the proximal and distal aorta without insertion of a graft.

In order to avoid upper body hypertension and poor perfusion to the lower body during aortic occlusion, oxygenated blood has been delivered to the arterial system below the diaphragm by two methods. Gerbode[11] has recommended the use of a shunt from the left atrium to the femoral artery, while a temporary shunt from the left subclavian artery to the distal aorta has been used by Stranahan.[12]

Although in recent years it has been shown that surgical management of traumatic aneurysms can be done with a low mortality,[13] and rupture of aneurysms has been reported to occur as long as eight years after injury,[14] there is a place for nonoperative treatment. Steinberg[3] reports one patient alive with an aneurysm 27 years after injury. In the poor-risk patient, observation is indicated if the aneurysm is stable and asymptomatic.

Historical Background

Vesalius in 1557[15] first recorded a case of traumatic thoracic aneurysm. He made this diagnosis when two physicians presented him with a patient who had a posterior thoracic pulsating mass. There was a history that the man had been thrown from a horse some years earlier. The diagnosis was confirmed at autopsy.

Apparently the next described case of chronic aneurysm after thoracic injury is that of Heller in 1904.[16] A thirty-seven-year-old man fell while carrying a heavy weight that landed on his chest. Eight months later the man died of heart failure. At autopsy, two transverse partial tears of the ascending aorta were found, one of which had dissected and loosened one of the aortic cusps, giving rise to aortic insufficiency.

Shennan[17] in 1929 described a pedestrian who was struck by a bicycle and then developed an aneurysm that ruptured into the esophagus eight weeks later.

In 1948 Stryker[18] noted a traumatic saccular aneurysm with involvement of bacterial endarteritis.

Hollingsworth[19] in 1952 emphasized that post-traumatic aneurysms most frequently arise distal to the subclavian artery, and this diagnosis was entertained if persistent widening of the mediastinum appeared after an automobile accident.

Etiology

In 1947 Strassman[1] found 72 cases of traumatic aortic rupture in a series of 7000 consecutive autopsies at a city general hospital. The most common cause was automobile accident; but it is interesting to note that there were more pedestrians with this injury than passengers. Falls and crushing injuries were other causative factors.

Parmley[2] et al. collected 296 cases of nonpenetrating traumatic aortic injury. They found that 80% expired immediately and approximately 15% died of bleeding after admission to the hospital. About 5% were patients that survived an aortic tear and developed a false aneurysm.

DeBakey[20] has stressed that destruction of the medial layer leads to aneurysm, be it by degenerative disease or trauma. This medial injury may not be readily apparent. Suspecting aortic rupture Eiseman[21] explored a patient with chest-wall injury and found only diffuse subadventitial ecchymoses without bulging of the vessel wall. However, the patient went on to develop aneurysm.

Although blunt trauma to the chest wall seems to be a common denominator for all traumatic thoracic aneurysms, deceleration has been given 'credit' as a causative factor.[22,23] However, carefully documented cases of deceleration injury without chest-wall trauma have not been recorded.

Biomechanics and Experimental Aneurysm Production

In 1918 Oppenheimer[24] studied the bursting pressures of the normal aorta and found that a pressure of over 1000 mg. Hg. would not cause rupture. Lloyd[25] noted a high incidence of cardiac and vascular injuries

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when he studied the effect of closed-chest injury on the bronchus. Stapp[26] in 1957 found that the hog's aorta could be ruptured by having the hog's chest strike a conventional steering wheel.

In 1944 Hass,[23] after studying aircraft accident victims, believed that unequal rates of deceleration of various body parts resulted in great stress at the point of connection.

Cammock[27] believed that when blunt trauma to the chest occurred, the sternum was brought into contact with the vertebral column and the heart was displaced into the left chest, exerting various stresses on the aortic wall. The tear extended from the intima towards the adventitia because maximal stress was at the inner vessel wall. Because the elastic limit of the adventitia was less than that of either the media or the intima, the rupture did not need to be complete.

Moffat, Silbergleit, Robert and Berkas[28] in 1965 have shown that a single blow to the dog's midsternum can cause a transverse aortic tear that will later give rise to aortic aneurysm.

Summary

Aortic aneurysm may be a result of major blunt-chest trauma. The recognition of a progressive aneurysm followed by a planned operative repair can result in the salvage of a person with a single correctable defect.

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12-28 May be secured from the author or the reprints.

When you are getting kicked from the rear it means you're in front.
— Bishop Fulton Sheen

A man who cannot lead and will not follow invariably obstructs.
— From Jacob Braude's "Speaker's Encyclopedia"

Advances

Hyperventilation

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Hyperventilation is a common syndrome which generally has a chronic course with recurring acute exacerbations. There is a tendency to simulate grave organic disease. This syndrome is caused by organic or psychogenic factors or a combination of both.

Most often the patient's complaint implicates the cardiovascular system. Next in frequency are the neurological, musculoskeletal, gastrointestinal, and respiratory systems. Psychiatric symptom complexes are less frequently encountered. (See Table 1.)

Lewis reported 50 cases of hyperventilation syndrome. In only one of these many cases was the diagnosis of hyperventilation made prior to admission to the hospital.[1] Peripheral paresthesia was the most consistent symptom. Disorder of breathing was the most common sign. Psychiatric disorders were the only instances in which the apparently correct diagnosis of hyperventilation was made prior to admission to the hospital.

Symptoms and Diagnosis

The diagnosis of hyperventilation is confirmed by inducing an acute exacerbation of the typical syndrome with a few minutes of voluntary overbreathing. The symptoms which develop are followed by marked apprehension and more hyperventilation. The apprehension in addition stimulates neuroendocrine mechanism and thus the cycle is complete and repeats. Tetany may result because of decreased ionization of calcium caused by the alkalinity of the intracellular fluid. In severe respiratory alkalosis convulsions may result.

Hyperventilation often produces unilateral symptoms such as numbness, tingling, weakness, muscle pain, and spasm. These symp-

TABLE I
Manifestations of Hypertension

- Cardiovascular System
  - Coronary rheumatic heart
  - Hypertension
  - Congenital heart
  - Acute rheumatic fever
  - Core pulmonale
  - Paroxysmal auricular tachycardia
- Neurological
  - Epilepsy
  - Brain tumor
  - Poliomyelitis
  - Cerebral vascular accident
- Respiratory System
  - Asthma
  - Emphysema
  - Respiratory tract infection
- Gastrointestinal
  - Cardiospasm
  - Peptic ulcer
  - Cholecystitis
  - Cholelithiasis
- Musculoskeletal
  - Rheumatoid synovitis
  - Myositis
  - Arthritis
- Endocrine Disorders
  - Islet cell tumors of the pancreas
  - Pheochromocytoma
  - Hyperthyroidism
  - Hypothyroidism
  - Insuline reaction
- Psychiatric Disorders
  - Nerves
  - Functional disorders
  - Hyperventilation

Continued

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toms are more apt to occur in the upper extremities but may involve half of the body, and they tend to occur on the side opposite the dominant side, that is, the left side in most cases. Sixteen per cent of 90 volunteers showed pronounced inequality of symptoms beginning unilaterally. About the same percentage showed decreased strength by grip dynamometer, averaging 14 pounds difference.[6]

The Mechanism of Production

Psychic Factors

The psychic pattern of hyperventilation begins with a precipitating process such as some somatic or psychic factor. Carbon dioxide deficit results. The increased output of carbon dioxide is followed by a decreased carbonic acid, a rise in serum pH and a diminution in plasma bicarbonate. The kidneys excrete sodium and potassium as bicarbonate and the carbon dioxide combining power is thus lowered.

Alkalosis

The degree of alkalosis can be maintained for many hours without effects.[2] After 60 minutes of hyperventilation at what appears to be normal depth of respiration, two or three deep breaths precipitated carpopedal spasm. Okel[2] noted no change in serum calcium. However, the inorganic phosphorus decreased and the carbon dioxide combining power decreased from 20.3 mq. per liter to approximately 13 mq. per liter in four volunteers.

Drop in Carbon Dioxide vs. Symptomalogy

In 1942 Davis and Wallace offered the hypothesis that the electroencephalogram slowing during hyperventilation was due to phasic vascular constriction with ischemic anoxia. Gibbs et al., taking exception to Davis' hypothesis, insisted that the electroencephalogram change was due to a decrease in cerebral carbon dioxide tension. This implied that there was a lack of some specific property of carbon dioxide per se on the nerve cells and cell membranes.

The Fall of Arterial Carbon Dioxide Tension vs. the Electroencephalogram

The mechanism of action was thought to be due to cerebral ischemic anoxia resulting from hypocapnic cerebral vascular construction, lack of some specific property of carbon dioxide per se on nerve cells and membranes, or to some effect of cerebral alkalosis.[5]

Effect of Hyperventilation

Using the nitrous oxide technique, Ketty and Schmidt[4] showed that the effect of hyperventilation on cerebral blood flow was a diminution of cerebral blood flow but no change in cerebral oxygen consumption. The blood flow was decreased 35 per cent. Meyer and Goth[5] made the conclusion, based on the concurrent recordings of the electroencephalogram, cortical blood flow, oxygen tension, carbon dioxide tension, and pH from several areas of the brain, that the electroencephalogram slowing in monkeys during hyperventilation was the result of hypocapnic constriction of cerebral vessels resulting in decreased cerebral blood flow and ischemic anoxia and not due to lowering of the brain's carbon dioxide tension. McHenry also noted no change in the cerebral metabolic rate with hyperventilation whether the subject was awake or anesthetized. There was a progressive drop in the venous oxygen content which paralleled to a certain extent the falling cortical tension, but without reaching critical oxygen levels.[3]

Oxygen Tension

Simultaneous evaluations were made of the oxygen tension by oxygen electrode, carbon dioxide tension with a carbon dioxide electrode, pH, sodium and potassium ions with glass electrodes, reflection oximeter for oxygen saturation, electroencephalogram and expired carbon dioxide as measured by infrared gas analyzer. The only measured factor[5] which had any statistical correlation with electroencephalogram flowing in response to hyperventilation was oxygen tension of the internal jugular vein. The thresholds of jugular oxygen tension for electroencephalogram slowing were distributed throughout a narrow range of about 21 mm. of mercury while the jugular pressure of carbon dioxide and jugular pH were scattered widely above and below normal values.

One of the cases studied was a Pickwickian syndrome in which a 16-year-old girl with carbon dioxide narcosis and obesity had extremely high jugular carbon dioxide tension of 75 mm. of mercury. Electroencephalogram slowing occurred at 22 mm. of mercury oxygen pressure in the jugular vein. Goth[5] did not believe that the lack of carbon dioxide was a primary cause of electroencephalogram slowing during hyperventilation. It was further noted that electroencephalogram slowing appeared during hyperventilation with 100% oxygen if the cerebral venous oxygen tension fell below the threshold; it just took longer.

Carbon Dioxide Tension

The cerebral venous flow was proportionately reduced with decreases in the blood carbon dioxide tension. Measured by thermo velocity the decrease was 30 to 40 per cent. The pH change during hyperventilation of +0.085 units decreased the release of oxygen from hemoglobin and resulted in tissue hypoxia. This is known as the Bohr effect. Relative decreases of the jugular oxygen tension were 27.1 per cent Bohr effect and 73 per cent as a result of the decreased cerebral blood flow during hyperventilation.

Below the age of 35 the cerebral vascular constrictive response to hypocapnia is more active than in the older group. The Bohr effect remains the same in both old and young individuals. Thus the electroencephalogram slowing with hyperventilation was more frequent in younger subjects and decreased with advancing age. However, the threshold of cerebral venous oxygen tension at which electroencephalogram slowing appeared was the same regardless of age.

Occlusive Vascular Disease

The presence of occlusive vascular disease did not abolish cerebral vasomotor reactivity, nor did it reduce it more than the age process itself accounted for. A-V malformation resulted in less reduction of cerebral venous oxygen tension because of shunting of the oxygen. Epilepsy caused no variation of the changes. Carbon dioxide narcosis eventually resulted in lowering of the jugular oxygen tension and the electroencephalogram slowing at the threshold oxygen tension.

The anoxic threshold for electroencephalogram slowing in a man with hyperventilation was approximately 21 mm. of mercury in the cerebral venous oxygen measurement. Similar studies without hyperventilation showed that the loss of electroencephalogram pattern occurred at 19 to 20 mm. of mercury, jugular oxygen tension unconsciousness at 16 to 17 mm. of mercury.

Minimal partial pressure of cerebral venous oxygen during hyperventilation showed a maximal reduction of cerebral blood flow in man as compared to controls. The maximal reduction of cerebral blood flow was 60 per cent by hyperventilation. The oxygen saturation fell approximately 30 per cent in man.

Treatment

For treatment of hyperventilation a simple and direct program is effective in 70 per cent of the patients who have demonstrated the symptomatology. An explanation of the physiologic basis for the symptoms is effective. Twenty per cent of the patients[1] achieved partial improvement and only ten per cent were unaided because of what was thought to be depression or hysteria.

References

1. Lewis, B. I.: Chronic Hyperventilation Syndrome. JAMA 155:1204, 1954.
2. Okel, B. B., and Jurst, J. W.: Prolonged Hyperventilation in Man, Associated Electrolyte Changes and Subjective Symptoms. Arch Intern Med (Chicago) 108:757, 1961.
3. Mc Henry, Slocum, Bivens, Mayes, and Hayes: Hyperventilation in Awake and Anesthetized Man. Arch Neurol 12:3, 1965.
4. Kety and Schmidt: Effects of Hyperventilation on Cerebral Blood Flow. Amer Neurol Association Transactions, 1964.
5. Gotoh, Meyer, and Takagi: Cerebral Effects of Hyperventilation in Man. Arch Neurol April, 1965.
6. Tavel: Hyperventilation Syndrome in Unilateral Somatic Symptoms. JAMA January 25, 1964.

When you are an anvil be patient; when a hammer, strike. — Arabian Proverb

The Net-Net Lease

With property taxes and maintenance increasing substantially and constantly in recent years, it has become increasingly difficult to write a long-term lease assuring a property owner an equitable return on his investment. In many cases, taxes and maintenance have doubled — and occasionally tripled over a five-year period. In addition, it is generally necessary to estimate these costs even prior to construction, and these estimates will frequently vary as much as 25 to 50% from actual experience after the project is in operation.

The first trend toward a solution of this problem was an "escalator clause" for rent. Basically, this clause provides for the adjustment of rents upward whenever property taxes exceed a certain amount. This requires frequent adjustment of rent and generally results in one or two years of operation at low profit or a loss due to the time lag between assessment of taxes and adjustment of rents.

As an obvious and simple solution to a problem severe enough to result in the occasional bankruptcy of a landlord, the "net-net lease" has come into popular use in recent years. This type of lease is not a new idea, but its use until recently was pretty much limited to very large ventures such as multimillion dollar buildings in large metropolitan areas.

Basically, the "net-net lease" provides for the payment to the facility owner of a fixed rental based upon a percentage of original investment in land and buildings. In addition, the tenant assumes the liability for all taxes, insurance, utilities and maintenance. Under this arrangement, the owner is not liable for anything except amortization of any debt on the facility.

The landlord's cash position can be readily determined by comparing rental receipts to mortgage payments. His tax position can be determined by reducing rental receipts by the known figures for depreciation and interest.

Rental rates on this type of lease vary with the term of the lease. Generally about 9% of original investment is maximum on a five-year lease, 8½% on a ten-year lease and 8% on a fifteen to twenty-year lease.

To illustrate the simplicity of such a lease, assume the owner invests $30,000 in land and an additional $90,000 in building for a total of $120,000. He leases it on a ten-year basis at 8½% "net-net." The tenant pays *all* expenses including utilities, repairs, taxes, insurance and janitorial service; and in addition, pays the owner $10,200 annually. The lease provides the same default provisions for failure to pay all expenses as standard leases provide for nonpayment of rent.

Assume further that the owner has a twenty-year mortgage for $80,000 at 5½%. His *cash* position is $10,200 rental receipts less $6,605 mortgage payments. *Taxwise*, his $10,200 rentals are offset by average annual interest of $3,600 and maximum tax depreciation averaging $3,000. His average taxable income during the first ten years will be about $3,600 or 3%. His true economic yield will be $10,200 less estimated depreciation of 2%, or $1,600, based upon projected economic market value at the end of ten years, or $8,600 (7.2%).

While this approach is very logical for large single-tenant properties such as drug stores, grocery stores, filling stations and other commercial properties, it is generally not too well suited for multiple-tenant projects due to the problems of apportioning taxes, insurance and other expenses. It can, however, have application where, for example, one member of a partnership owns a building which he rents exclusively to the medical partnership.

Such leases can also be used in conjunction with about all "option-to-purchase" arrangements.

If you now own or are considering purchase of a rental facility, this rental technique may be "tailor-made" to assure you a constant equitable return on your investment.

William D. Huntington*
Minneapolis, Minnesota

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*Northern Division Manager, Professional Management Midwest.

Big Mountain Medical-Ski Conference — 1966

Hope you will plan now to join us January 26, 27 and 28, at the Big Mountain, Whitefish, Montana. The scientific program will again be restricted to the evenings (7-10 P.M.), so that you may enjoy the whole day skiing. Special entertainment will be arranged for the wives — during each evening's program. Reservations for lodgings should be made direct with: The Big Mountain, Whitefish, Montana. AAGP credit.

R. D. Buchanan, M.D., President
Northwestern Component M.A.G.P., Box 220, Columbia Falls, Montana

So live that after the minister has ended his remarks, those present will not think they have attended the wrong funeral. — The Mortarboard

Abstracts, Briefs and Commentaries

CERVICAL SPINE INJURY

Abel has stated that routine views of the cervical spine are of little help in the proper evaluation of patients with relatively minor injuries — whiplash and other mild afflictions of the cervical spine. He did some experimental work on cadavers after dissecting away the neck muscles and placing the necks in a position comparable to a rear-end "whiplash" impact; from these experiments he was able to demonstrate that after the age of one year the deformities in the cervical spine are astonishingly frequent, and that they increase progressively with age. From these findings he concludes that such deformities are acquired and not congenital, as they occur in approximately eight per cent of those under the age of 21.

It has also been observed that the hypertrophic changes in the bodies of the vertebrae occur independently of hypertrophic changes in the apophyseal joint and vice versa.

It is suggested that the hypertrophic changes in the bodies of the cervical vertebrae are largely a response to static weight-bearing stresses, whereas apophyseal joint arthritis is a response to dynamic stresses resulting from the alterations in the planes of motion.

Changes and alterations in any part of the suspension system, which includes the vertebral bodies, the intervertebral discs, and the lateral joints of Luschka and the apophyseal joint, are of the same suspension system, so that the alterations in one of these must eventually be communicated to the others.

Abel indicates that the symptomatology of neck strain is quite variable, both immediately after the injury and some years later. He stresses the value of specialized views of the lateral masses in order to demonstrate the characteristic deformity.

It has been stated by Severy Mathewson and Echtol that the load to the head may exceed 100 pounds for rear-end collisions not exceeding 15 miles per hour, and a peak load of 150 pounds has been recorded in collisions at 10 and 20 miles per hour.

The most frequently observed cervical fractures in these experimental studies by Abel were observed in the interarticular isthmus and lamina of one or more of the lower cervical vertebrae, fractures of the lower process of C1 and/or C2, and fractures of the elements of the joints of

Continued

Luschka. These three types of fractures were not visualized in routine views of the cervical spine.

The cervical spines of twenty-eight cadavers of elderly males and females were anatomically compared with the cervical spines of thirteen females under twenty.

On a statistical basis the authors hypothecated that there was an increased asymmetry of the lateral cervical articular masses with an increase in the age of an individual. He suggested that this chronic remodeling process may be accelerated by post-traumatic changes in the tissues of the surrounding joint capsule or by repeated and prolonged stresses associated with exertion or posture.

Abel found no consistent relationship between the narrowing of the disc space and the apophyseal arthritis at the same vertebral level, because other disc spaces were narrowed without associated arthritis. No consistent relationship was found to exist between disc-space narrowing and asymmetry of the articular masses of the C 4-6 segments.

He concluded that the asymmetry is due to a continuing remodeling in the response to dynamic effect of trauma and the stresses of weight bearing and exertion, causing it to become progressively more accentuated with time.

NOTE: One might question some of Abel's clinical hypotheses, e.g., that whiplash neck strain without appreciable immediate symptoms can be a factor in delayed symptoms in the neck years later. He has, however, made a good case for fractures of the cervical bodies which were ordinarily not visualized in the routine x-ray; and certainly if an acute fracture can be found following injury, one must then accept the cause and effect relationship. If one refers to the dynamic action of physical wear and tear as a common etiologic factor in the development of the changes in the cervical vertebrae, then it would seem more logical that these changes, as observed by Abel with greater frequency through advancing age, could account for the eventual neck pain after relatively minor injury. To account for these changes on the basis of one specific incident would seem to be less likely.

In using the term "dynamic effect of trauma" Schoening probably did not intend to indicate a specific incident of injury. He appears to have proven that the asymmetry of the cervical articular masses is a progressive change observed with advancing age.

One is then left with a dilemma, and it seems most logical to conclude that hypertrophic changes in the cervical spine do appear more often with advancing age and can be a cause of neck pain with or without injury; and also that an incident of strain could be superimposed upon such hypertrophic changes, so that the finding of a recent fracture in the pillar views of the cervical spine following injury must be attributed to the incident.

Carl O. Rice, M.D.
Minneapolis, Minnesota

Abel, Martin S.: Radiologic Aspects of Moderately Severe Cervical Spine Trauma. Schoening, Herbert A.: A Radiologic Study of the Changes of Shape of the Cervical Articular Masses with Age. Arch Phys Med 44:303, 1963.

Abel, Martin S.: Radiologic Aspects of Moderately Severe Cervical Spine Trauma. Arch Phys Med 40:371, 1959, and Moderately Severe Whiplash Injuries of the Cervical Spine and their Roentgenology Diagnosis. Clin Orthop 12:189. J. B. Lippincott Co. 1958.

HYPERTROPHIC GASTRITIS

Giant hypertrophic gastritis was first described in 1888 by Menetrier; since then more than 100 cases have been recorded. Great interest was aroused in later years, owing to excessive loss of albumin through the gastric mucosa, as instances of idiopathic hypoalbumin anemia were found to be due to this disorder. It is important to determine the site of albumin leakage; likewise it is important to determine if the disease in the stomach is due to tumor or inflammation. The writers describe a case of giant hypertrophic gastritis with excessive albumin leakage.

Case Report:

A male, 64 years of age, with achylia and periodic edema of the legs for 20 years is the basis of this report. He developed acute abdominal pain, return of marked edema, voluminous vomiting of mucus, and fatigue. The serum concentration of protein and albumin was extremely low. Intravenous R.I.H.S.A. showed the half life of albumin to be very short; x-ray of the stomach revealed exaggerated mucosa and signs of malignancy. Surgical removal of some of the suspected area disclosed only inflammation.

The patient was treated conservatively for two months with diet and diuretics with little improvement. A Bilroth I gastric resection was performed, the proximal incision being through changed tissue. The patient then improved promptly with normalized serum proteins and increased half-life albumin. Roentgen examination revealed great improvement in the remaining stomach.

The authors have gone into great detail regarding the chemistry, histology, and symptom improvement. Graphs and photographs are excellent. All of these are available for the internist or surgeon who wishes to obtain more complete information.

Discussion: The rarity of this disease is established. The review represents a great deal of effort for which the authors should be complimented.

Stanley R. Maxeiner, Sr., M.D.
Minneapolis, Minnesota

Hansson, R., Lundh, G., and Skold, G.: Giant Hypertrophic Gastritis Treated with Gastric Resection. Acta Chir Scand 129: 1965.

OVARIES AND CORONARY DISEASE

To test the hypothesis that functioning ovaries are responsible for the relative degree of female protection against coronary heart disease, 2 groups of women, one with bilateral oophorectomy, the other with hysterectomy, were examined. All had been operated upon between 10 and 25 years before and had been under the age of 45 years at the time of the operation. Detailed comparisons of the 2 groups of examined women (267 oophorectomized and 385 hysterectomized) indicated that they were strikingly similar in most respects. The prevalence rate for coronary heart disease was 8% for both groups. These findings suggest that some factor or factors apart from ovarian function is responsible for the relative freedom from coronary heart disease among women as compared with men.

Courtesy of References and Reviews
Journal of the American Medical Association

Ritterband, A., Jaffe, I., Densen, P., Magagna, J., and Reed, E.: Circulation 27:237, 1963.

THE TREATMENT OF INOPERABLE CANCER WITH RADIOISOTOPES

The management of inoperable carcinoma always presents a problem. Ariel has described a technique of administering isotopes intra-arterially, either through the femoral arteries for generalized abdominal lesions or through other vascular systems for more accurate localization.

The author makes no exaggerated claims for its value; but he states that it has been well tolerated and he believes that some patients have enjoyed increased longevity and others, some palliation.

Yttrium 90 was the radioactive element used in his series, having a half life of 61 hours.

Carl O. Rice, M.D.
Minneapolis, Minnesota

Ariel, Irving M.: Treatment of Inoperable Primary Pancreatic and Liver Cancer by Intra-arterial Administration of Radioactive Isotopes. Ann Surg 162:267, 1965.

AMYOTROPHIC LATERAL SCLEROSIS

Study of the onset and course in 70 fatal cases of amyotrophic lateral sclerosis demonstrated that the onset was either atrophic or spastic, in either the bulbar or the spinal area. Regardless of the type and area of involvement, spastic forms nearly always become also atrophic and atrophic-spastic, while spinal involvement spreads to bulbar, and bulbar to spinal areas, if the patient lives long enough. A few cases of purely atrophic disease were found and still fewer of purely spastic disease. These forms represent thus a single degenerative disease, a spectrum having the atrophic process (progressive muscular atrophy) at one end, the spastic (primary lateral sclerosis) at the other, and a combination (amyotrophic lateral sclerosis) in the middle. With time, cases at each end of the spectrum move toward the center. On the average, with considerable spread, the patients reported died 36 months after the onset of spinal spastic sclerosis, 33 months after the onset of spinal atrophic, 24.6 months after the onset of bulbar spastic, and only 17 months after the onset of bulbar atrophic involvement. Since death practically always results from bulbar involvement, life may last almost indefinitely, so long as purely spinal changes exist in this disease.

Courtesy of References and Reviews
Journal of the American Medical Association

Mackay, R.: Arch Neurol 8:117, 1963.

THE SUDDEN MURDERER

Clinical observation of 43 "sudden murderers" indicated that most of them suffered from a constant conflict between inner feelings of inadequacy and isolation, and conscious needs to succeed and conform. Especially when these persons were at the threshold of a meaningful life adjustment, this conflict created an increasing sense of self-doubt, tension, and repressed rage, culminating in explosive violence. The importance of sustained professional contacts with such patients, even during periods of apparent conformity and adequacy, is stressed.

Courtesy of References and Reviews
Journal of the American Medical Association

Blackman, N., Weiss, J., and Lamberti, J.: Arch Gen Psychiat 8:289, 1963.

PATIENTS WITH THREE OBSTETRIC COMPLICATIONS

The purpose of this investigation was to determine the relation between three obstetric complications and certain psychiatric symptoms and personality characteristics as measured by the Minnesota Multiphasic Personality Inventory. One hundred sixty-nine white, unmarried primigravidas living at a home for unwed mothers were given the Minnesota Multiphasic Personality Inventory at the beginning of the third trimester. Three obstetric complications were studied: Premature rupture of the membranes, excessive weight gain, and pre-eclampsia. On the basis of the Minnesota Multiphasic Personality Inventory given again before delivery, patients who experienced any of these three complications were more withdrawn, anxious, and concerned with their bodily functions than those who did not develop them. The patients with premature rupture of the membranes exhibited the least pathology; however, they were more withdrawn than the control group. The patients with excessive weight gain were more anxious, distrustful, passive, dependent, and aware of their bodily functions than the control group. The group with pre-eclampsia, like the excessive-weight-gain group, showed greater concern for bodily functions and, in addition, seemed to use physical symptoms as a means of solving personal difficulties. The excessive-weight-gain and pre-eclamptic groups thus overlapped in some personality characteristics and were generally more disturbed than those patients who experienced premature rupture of the membranes. This investigation supported previous findings that women who develop pre-eclampsia or who become excessively overweight early in pregnancy frequently exhibit psychopathology.

James Janecek, M.D.
University of Minnesota

McDonald, R. L.: Personality Characteristics in Patients with Three Obstetric Complications. Psychosomatic Med 27:383, 1965.

LYMPHATIC DRAINAGE OF THE BREAST

Studies done by Halsell et al., in which they injected sky-blue dye directly into the intradermal tissue about the nipple areola, reveal that the dye enters the lymphatic through a few selective trunks from the primary injection site and thereafter courses toward the axilla. From this superficial position the lymphatic progresses to deeper tissue, suggesting that the more peripherally situated portion of the skin flap is farther away from the lymphatic channels than that of the areola.

It might have proven additionally valuable to have made the initial injection of the dye in the depth of the breast substance adjacent to the tumor, simulating thereby more nearly the lymphatic drainage from a malignant lesion lying within the breast substance rather than in the interdermal tissue of the areola.

Carl O. Rice, M.D.
Minneapolis, Minnesota

Halsell, John T., Smith, James R., Ventlage, Charles R., Park, Oakley K., and Humphreys, James W.: Lymphatic Drainage of the Breast Demonstrated by Vital Dye Staining and Radiography. Ann Surg 162:221, 1965.

LUMBAR SYMPATHECTOMY

The results of 198 lumbar sympathectomies, performed upon 133 patients (average age 60 years) with various peripheral vascular diseases, are evaluated. The diseases included arteriosclerosis obliterans, diabetic gangrene, embolism-thrombosis, thrombophlebitis, frostbite, and causalgia. In 90 patients arteriography was performed at the time of sympathectomy, which has been discontinued as a routine procedure since 2 of the deaths in the series were directly attributable to the arteriography. Correlation of good results with arteriography was possible in 73% of cases. Amelioration or relief of symptoms occurred in 79% of cases. The morbidity rate was 2%, and mortality was 3.5% (increased by arteriography). Amputations were required in 30%. The authors feel that lumbar sympathectomy remains a valuable procedure in selected cases of peripheral vascular diseases, particularly those which are primarily vasospastic in nature or in which the arterial obstructive process is not too advanced and extensive. The routine use of common iliac arteriography is not recommended, but it should be judiciously applied in selected cases.

Courtesy of References and Reviews
Journal of the American Medical Association

Palumbo, L. and Lulu, D.: Arch Surg 86:512, 1963.

HOMONYMOUS HEMIANOPIA

The role of the quantitative study of visual fields in the diagnosis of topical neurologic disorders was studied in 100 patients with homonymous hemianopia, who were examined by tangent screen techniques and a projection perimeter. One-fourth of the hemianopias were produced by temporal lobe lesions, usually occurring in the younger age group and equally distributed between the 2 sexes. The most frequent etiologic factor was a neoplasm. Except when there was also parietal lobe extension, the optokinetic response was normal. In one-third of this series the hemianopia had originated in parietal lesions, which occurred in an older age group and apparently more frequently in men than in women. The optokinetic nystagmus, present in 28 cases in this series, was of great diagnostic value, for not a single patient with parietal lobe hemianopia showed normal optokinetic response. Occipital lobe lesions, the most common casue of hemianopia, was the etiological factor in two-fifths of the patients studied, occurred mainly in the older age group (50 years was the average age) and was found more frequently in men than in women. In contrast with temporal lobe lesions, the occipital lobe defects originated in vascular lesions rather than in tumors, in a 3/1 ratio. The optokinetic sign, usually negative, was positive in 7 patients. Two arteriovenous malformations were detected, in each case associated with a mass lesion. Visual acuity was within normal limits in the entire series, indicating that a patient can see 20/20 with one half of the macula.

Courtesy of References and Reviews
Journal of the American Medical Association

Smith, J. L.: Amer J Ophthal 54:616, 1962.

Men are born with two eyes, but with one tongue, in order that they should see twice as much as they say. — C. C. Colton

The desire to take medicine is perhaps the greatest feature which distinguishes man from animals. — Harvey Cushing

Book Reviews

Character development is the great, if not the sole, aim of education. — O'Shea

SURGERY OF THE BILIARY PASSAGES AND PANCREAS — **Dr. Walter Hess, Van Nostrand Company, Princeton, New Jersey.**

This is a very thorough book of 624 pages containing opinions and advice of the author based on a large personal series, and his own evaluation of literature on this subject.

The author is clinical professor of surgery at the University of Basle, Switzerland. He was formerly professor of surgery at the Medical School of the University of Alexandria, Egypt.

The book contains good anatomic operative drawings of technique and pathology. Reproductions of x-rays have line drawings adjacent as an excellent method of explanation.

The section on postoperative complications presents many of the problems of biliary and pancreatic surgery, and suggestions for their management. The author emphasizes his own concept of a complete intraoperative diagnosis, and as part of this concept has a large section on radiomanometry after the method of Caroli. This is described as a careful and detailed method of investigation of the biliary duct system at the time of surgery. The reviewer recommends a careful study of this section.

Surgery relative to the sphincter of Oddi and the problems of chronic pancreatitis seem to omit some of the methods currently popular in American surgery, but is otherwise quite complete.

The book makes an excellent text for this subject, covering sufficient background material of anatomy, physiology, pathology, and has an adequate index and quite extensive coverage.

J. H. Strickler, M.D.
Minneapolis, Minnesota

CONGENITAL HEART DISEASE — **Correlation of Pathologic Anatomy and Angiocardiography, Edwards, J. E., Carey, L. S., Neufeld, H. N. and Lester, R. G.; W. B. Saunders Co., Philadelphia, 1965; 890 pages, 2 volumes, price $45.**

Congenital heart disease in this two-volume work is subtitled Correlation of Pathologic Anatomy and Angiocardiography; however, the correlation includes far more than pathology and roentgenology, considering all the major clinical aspects of congenital heart disease. This is an unusual if not a unique work. The authors have started with a simplified outline of congenital heart disease, covering the subject under five headings: increased pulmonary arterial vasculature with cyanosis present; increased pulmonary arterial vasculature with cyanosis absent; decreased pulmonary arterial vasculature with cyanosis present; normal pulmonary arterial vasculature with cyanosis absent; and pulmonary venous obstruction. This is mainly a clinical outline, and pathologic entities appear in several sections, as, for instance, the same disease with or without cyanosis. The outline is closely followed, starting with typical illustrations of various entities and ramifying into a thorough study of associated defects. The typical treatment of each entity includes a detailed anatomical description with minimal text and maximal use of illustration in black and white, followed by a brief description of the clinical features and altered physiology. The radiographic and angiographic material is then presented in profuse illustrative detail, followed by correlation of roentgenographic and post-mortem anatomy.

The text throughout is pared to the lean heart of the matter. Bibliography is sparse and intermingled throughout the text.

The work emphasizes the essential role of roentgenology in the clinical evaluation of congenital cardiac problems (equally true in many acquired cardiac problems as well). The clinician would like to see a fuller treatment of other clinical features, especially electrocardiography and catheterization data.

Doctor Edwards et al. have obviously drawn upon an enormous wealth of material to illustrate in such detail the panorama of congenital heart disease. Withal, they have considered the reader's limitations and divided this massive work into two three-and-a-half-pound, fairly slim although outsized volumes, convenient to hold and suitable for large illustrations. The table of contents is deceptively simple with five items; the index is repeated in both volumes. These books are required reading for a large segment of the medical population: cardiologists, pathologists, and roentgenologists.

Reuben Berman, M.D.
Minneapolis, Minnesota

The Tobacco Tyrant*

Harf's Practical Therapeutics say: "Tobacco when smoked or chewed to any extent by young persons, stunts the growth of all parts of the body, and is very apt to cause in all users granular sore throat, pharyngitis, laryngitis and faucitis. Sometimes angina pectoris develops. "Tobacco Heart" is a term applied to a condition of this viscus characterized by disorders in its rhythm or power, palpitation, arrhythemia and dyspnea."

Shoemaker says: "Tobacco increases the excitability of the heart by a direct action upon its intrinsic ganglia. The spinal and cerebral centers become affected, and inco-ordination, a staggering gait and vertigo are prominant symptoms of the toxic action. Finally, collapse and death may occur from paralysis of the heart or of the respiration. Similar results also follow the inhalation of tobacco smoke, though generally they appear in a much milder form than when the drug is swallowed. Poisoning has followed the application of tobacco leaves to wounds."

Brunton says: that a sustained low blood pressure in the absence of tuberculosis, usually means excessive smoking.

E. O. Giere, M.D.**
Minneapolis, Minnesota

**Editor's Note: In 1928 Dr. E. O. Giere prepared and presented a manuscript at one of the Twin City hospitals on the evil effects of tobacco.*

***Through the courtesy of his sons, Doctors Richard and Joe Giere, the timeworn and faded manuscript was made available to the editor. Excerpts will be printed serially.*

See Minnesota Med 48:1376, 48:1518 and 48:1687, 1965.

Virtues of Human Parts

From Pliny we learn that various parts and products of the human body are credited with remarkable virtues. A few instances of remedies drawn from the human body are ear-wax or a powdered tooth against stings of scorpions and bites of snakes, a man's hair for the bite of a dog, the first hairs from a boy's head for gout. Simply tying two fingers or toes together is recommended for tumors in the groin, catarrh, and sore eyes. Or the eyes may be touched thrice with water in which the feet have been washed. Scrofula and throat diseases may be cured by the touch of the hand of one who has died an early death, although some authorities do not insist upon the circumstance of early death but direct that the corpse be of the same sex as the patient and that the diseased spot be touched with the back of the left dead hand.*

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*Thorndike, Lynn: A History of Magic and Experimental Science, Vol. 1, p. 82. The MacMillan Company, New York, 1923.

The Mouse Amulet

(Continued from page 100)

the mouth, and incontinence in children. For external use it was split open and applied to any part of the body requiring attention.

Long since, the original delusion that the mouse was imbued with the primal life force must have gone into limbo; however, the myth of the mouse's curative properties has persisted: a classic example of the continuance of practices long after the rationale of their genesis has been forgotten or discredited. Myths die hard!

A chip on the shoulder is too heavy a piece of baggage to carry through life.
— Forbes Epigrams

Special Article

An Outline of Basic Enzymology in Blood Clotting[*]

WALTER H. SEEGERS, Ph.D.
Detroit, Michigan

LIKE OTHER mechanisms in physiology the clotting of blood is of tremendous interest to the physician as well as to the basic scientist. In blood banking, surgery, pumping of blood, thrombosis, hemorrhagic diseases, nutrition, wound healing, and practically every phase of medical practice the phenomenon of blood clotting has to be dealt with expertly. This is therefore of such substantial consequence that education in this field is properly promoted with the greatest possible thoroughness and efficiency. During the past quarter century progress in the biochemistry of the blood-clotting mechanisms has been surpassed by no other developments when considered in the light of the unique insights gained, the complexity of the chemistry that has been elucidated, and the formidable difficulties that have been overcome. New examples of nature's ways have been discovered by the application of laboratory technology. The phenomenon of blood clotting need no longer be looked upon as a riddle but can be seen as one of the beautifully integrated systems in our physiology.

Descriptive Observations

Conditions that Retard Clotting

Removal of calcium ions is the most common and effective way to prevent clotting. This can be done by using a chelating agent[**] such as sodium citrate or ethylenediaminetetracetate. Oxalates form microcrystalline precipitates with calcium, while heparin leaves the calcium alone and blocks protein interactions. In like manner hirudin, obtained from the saliva of the leech, is an anticoagulant. Cooling blood, or centrifuging to remove the formed elements and especially the platelets, leaves the mechanisms of the plasma in a balanced state. Lack of vitamin K in the diet, or its faulty absorption due to bile-salt deficiency, is followed by a lowering of

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[*] From the Department of Physiology and Pharmacology, Wayne State University, School of Medicine, Detroit, Michigan. This investigation was supported by research grant HE 03424-08 from the National Heart Institute, National Institutes of Health, U. S. Public Health Service.

[**] See Test Your Word Score Page 97.

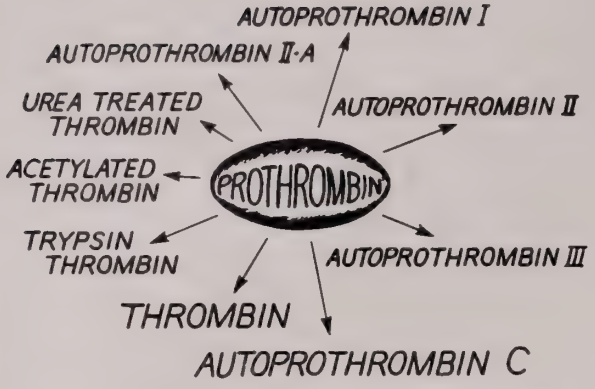
AUTOPROTHROMBIN I
AUTOPROTHROMBIN II-A
UREA TREATED THROMBIN
AUTOPROTHROMBIN II
ACETYLATED THROMBIN
PROTHROMBIN
TRYPSIN THROMBIN
AUTOPROTHROMBIN III
THROMBIN
AUTOPROTHROMBIN C

Fig. 1 — Prothrombin is a multipotential protein capable of breaking into subunits. These subunits are themselves active in the generation of thrombin activity. Thrombin and autoprothrombin C are each separate enzymes derived from prothrombin as end products, while autoprothrombin I, II, III, and autoprothrombin II-A are intermediate derivatives. Urea-treated thrombin, trypsin thrombin, and acetylated thrombin are modifications of the thrombin molecule. Acetylated thrombin does not clot fibrinogen but is an esterase.

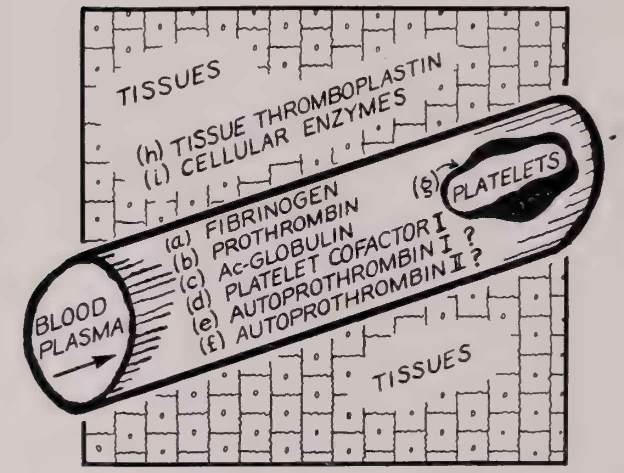
TISSUES
(h) TISSUE THROMBOPLASTIN
(i) CELLULAR ENZYMES
(g) PLATELETS
(a) FIBRINOGEN
(b) PROTHROMBIN
(c) Ac-GLOBULIN
(d) PLATELET COFACTOR I
(e) AUTOPROTHROMBIN I ?
(f) AUTOPROTHROMBIN II ?
BLOOD PLASMA
TISSUES

Fig. 2 — Diagram intended to emphasize that the potential environment needed for prothrombin activation resides in the plasma, platelets, and tissues. Prothrombin is in the plasma together with calcium ions, Ac-globulin (factor V), platelet cofactor I (factor VIII), and fibrinogen. The amount of autoprothrombin I (factor VII?) and autoprothrombin II (factor IX), which is in plasma, if any, is unknown on a quantitative basis. Both are derived from prothrombin when blood clots. The platelet materials are made available when the platelets undergo morphological change due to contact with surfaces, and/or thrombin. Tissue materials function following injuries that break the cellular structure.

plasma prothrombin concentration and reduced clotting power. Reduced liver function due to tissue pathology or inhibition of the metabolic machinery, as with dicumarol and related compounds, may be associated with restricted supplies of prothrombin in the blood plasma, and slow clotting of the blood. Lytic agents that are capable of destroying fibrinogen can eliminate the very possibility of fibrin formation. The surface characteristics of the vessel in which the blood circulates or into which it is received may either promote or retard clotting, depending upon the electric charge, hydrophobic and hydrophilic properties, and wettability. Paraffin-lined or silicone-treated glassware is perhaps the most commonly used surface for maintaining the normal fluidity of the blood.

Accelerated Clotting

Surface contact with many substances and especially gauze packs and tampons accelerate clotting. Gently agitating the blood or elevating the temperatures hastens clotting. Rapid clotting follows upon the addition of thrombin, tissue extracts, certain snake venoms, the enzyme autoprothrombin C, and several other enzymes.

Origin of Thrombin

With strong thrombin solutions it is possible to clot blood in less than one second. Normally plasma contains 300 times more thrombin than is needed for clotting in 15 seconds, but it is there in an inactive form. How does this dormant procoagulant power unfold itself when needed, and how does it do so at undesirable times, as for instance in thrombosis? This profound question in biology has been the topic of intense research since Alexander Schmidt first discovered prothrombin in the past century. From work with purified prothrombin and other purified components of plasma, several of the basic reactions are known. There may be a certain sequence in which these occur, but in general many reactions run their course at the same time. Despite these complexities, however, it is now possible to formulate an interpretation of the mechanisms of prothrombin activation in terms of enzymology. The key to the modern enzyme concept of blood clotting was the very nature of the prothrombin molecule itself. It was found to be a molecular system for which there was no prior model in the literature of biochemistry. In the prothrombin molecule itself reside the subunits that are needed for rapid thrombin generation (Figure 1). Prothrombin activates itself and needs only the proper environment for unfolding its clotting power.

Environment for Thrombin Generation

A most ingenious arrangement in our physiology consists of using three separate compartments for the distribution of the ingredients for creating the prothrombin activation environment. The three locations are the platelets, plasma, and somatic cells. The ingredients of platelets + plasma (intrinsic system) make an adequate combination of substances for thrombin generation, but clotting occurs only slowly. Platelets + plasma + cellular elements (extrinsic system) may give a combination or environment for rapid clotting. A break through the blood vessel wall thus provides the ultimate mobilization of procoagulant power because it calls upon the platelets, tissues, and plasma resources all at one time to furnish the environment which prothrombin needs for its activation (Figure 2). I shall then consider the recently developed perspective under three main divisions as follows: (1) characteristics of the prothrombin molecule, (2) subunits of the prothrombin molecule, and (3) conditions for the spontaneous activation of prothrombin.

Characteristics of the Prothrombin Molecule

The prothrombin molecule isolated from bovine plasma has a molecular weight of 69,000. With the electronmicroscope the particles are seen to be uniform when one molecule is compared to another (Figure 3). Many years ago I found that purified prothrombin would spontaneously convert to thrombin in certain strong salt solutions such as sodium citrate. Some years later, the experiment was repeated, and it was found that autoprothrombin C (thrombokinase) activity developed at the same time and at the same rate as thrombin. Thus it was discovered that

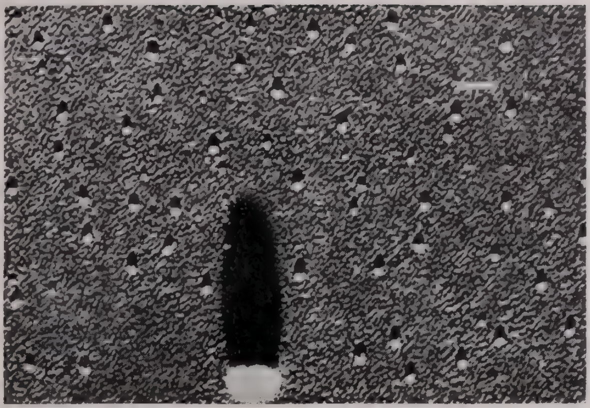

Fig. 3 — Shadow-cast electronmicrograph of bovine prothrombin produced by Jeanne M. Riddle. The white bar is a thousand angstrom units in length. The polystyrene latex standard has a diameter of 1380 microns.

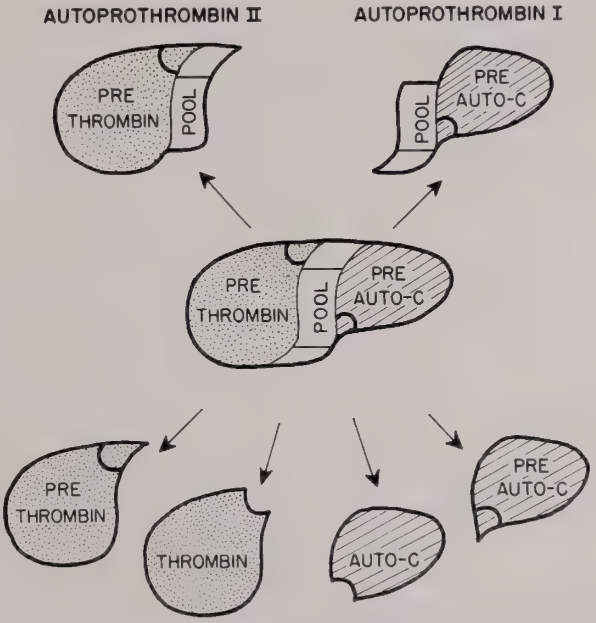

Fig. 4 — The prothrombin molecule contains the enzymes thrombin and autoprothrombin C, and in addition a "general" pool of protein material as well as carbohydrate. The molecule can be split in several different ways with the use of thrombin and autoprothrombin C. The diagram is supposed to suggest the nature of the substances isolated up to now. Note that the protein pool may associate with the prethrombin portion of the molecule or with the preautoprothrombin C.

the prothrombin molecule contains two enzymes, and that nothing besides prothrombin is actually needed to obtain these two enzymes. In one experimental stroke it was shown that all else concerned with prothrombin activation has to do with environmental conditions. Furthermore, it was found that other subunits of the molecule that can be produced are important in prothrombin activation (Figure 1). How are these subunits split from the original prothrombin, and what is their function in the generation of thrombin activity?

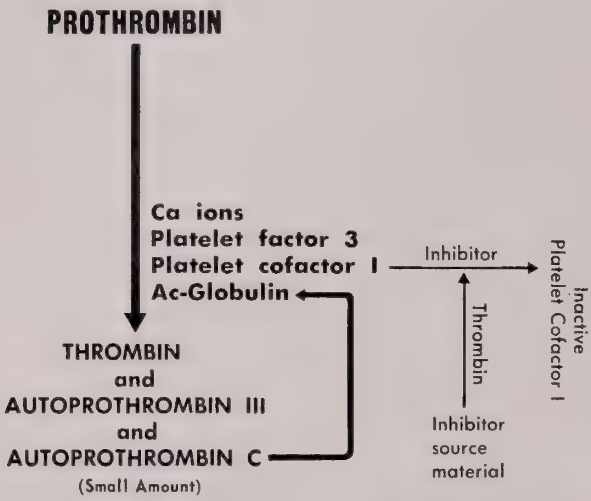
PROTHROMBIN
Ca ions
Platelet factor 3
Platelet cofactor I
Ac-Globulin
THROMBIN
and
AUTOPROTHROMBIN III
and
AUTOPROTHROMBIN C
(Small Amount)
Inhibitor
Thrombin
Inhibitor
source
material
Inactive
Platelet Cofactor I

Fig. 5 — Prothrombin activation can begin upon surface contact, whereupon there may be plasma changes as well as platelet dissolution. Thrombin reaction specificity is governed by Ac-globulin. The autoprothrombin C in the prothrombin remains mostly, if not entirely, in the precursor form called autoprothrombin III. Thrombin produces a lipid inhibitor from inhibitor source material that is neutralized by platelet cofactor I (factor VIII). This route of prothrombin activation is self-limiting.

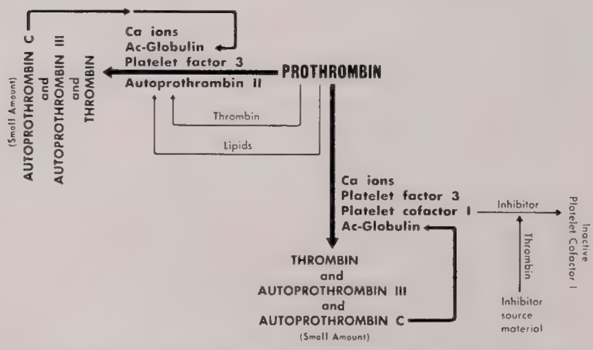
Ca ions
Ac-Globulin
Platelet factor 3
Autoprothrombin II
PROTHROMBIN
AUTOPROTHROMBIN C
(Small Amount)
and
AUTOPROTHROMBIN III
and
THROMBIN
Thrombin
Lipids
Ca ions
Platelet factor 3
Platelet cofactor I
Ac-Globulin
THROMBIN
and
AUTOPROTHROMBIN III
and
AUTOPROTHROMBIN C
(Small Amount)
Inhibitor
Thrombin
Inhibitor
source
material
Inactive
Platelet Cofactor I

Fig. 6 — The platelet-plasma activation of prothrombin involves autoprothrombin II which can be derived from prothrombin due to thrombin Autoprothrombin II (platelet cofactor II, PTC, factor IX, Christmas factor, hemophilia B factor) is in a sense a substitute for platelet cofactor I (factor VIII), but is not neutralized by the lipid from inhibitor source material.

Subunits of Prothrombin

As a crude device for purposes of education I have created an imaginative geometrical projection of the prothrombin molecule and some of its major subunits (Figure 4). To see how these are created and function in our physiology, six important questions can be asked, each one of which has been answered on the basis of experimental inquiry. What happens to prothrombin when added to the following:

Thrombin .... = ?
Thrombin + Ac-globulin (factor V) ...... = ?
Thrombin + Ac-globulin + lipid .... = ?
Autoprothrombin C .... = ?
Autoprothrombin C + Ac-globulin ...... = ?
Autoprothrombin C + Ac-globulin + lipids = ?

In the presence of the enzyme thrombin (M.W. = 33,700) the prothrombin substrate changes to autoprothrombin II (factor IX). This subunit, with a molecular weight 41,500, is not an enzyme but contains thrombin within its structure (question 1 is answered). Prothrombin also activates in the presence of autoprothrombin C (M.W. = 24,000 ?), but unlike the activation product with thrombin, another subunit called autoprothrombin I_c (M.W. = 34,000) is obtained. This is not an enzyme, but contains autoprothrombin C within its structure (question 4 is answered). By adding Ac-globulin (M.W. near 99,000 ?) a protein normally in plasma, the reaction specificity of the enzyme thrombin as well as the reaction specificity of the enzyme autoprothrombin C is changed, and the subunits of prothrombin which are produced are autoprothrombin III (preautoprothrombin C) and thrombin (questions 2 and 5 are answered).

Thrombin and autoprothrombin C by themselves specifically produce distinct activation products. In the presence of Ac-globulin the activation products are the same for each enzyme. *The function of Ac-globulin is to govern the reaction specificity of two enzymes: namely, thrombin and autoprothrombin C.* Ac-globulin is thus a coautocatalyst or a special coenzyme. Lipids, such as cephalin, by means of hydrophobic and hydrophylic molecular attraction and repulsion plus surface activity supply an environment for prothrombin to activate rapidly and do not change the end product (questions 3 and 6 are answered).

Physiological Integration for Spontaneous Activation of Prothrombin

Initiation of Prothrombin Activation

Prothrombin itself contains all that is required to have thrombin. It activates itself whenever it is in a suitable environment. Most likely minute amounts of thrombin generate at all times in our circulation and are disposed of by antithrombin. So one ought to speak of accelerated prothrombin activation rather than the initiation of such an event. In any case, tissue extracts are prominent procoagulants that can produce rapid acceleration. Platelets can disintegrate upon contact with glass, tissues, collagen, and other surfaces. Some evidence indicates that a special protein (factor XII) activates upon contact and supplies procoagulant power; however, patients with such a deficiency are not prone to bleeding. The main impetus for thrombin generation comes from platelets and tissues, while the prothrombin molecule itself is sensitive to surfaces including the lipids contained in platelets and the lipoproteins of tissues.

Plasma-platelet Activation Sequence

Upon suitable surface contact protein(s) alterations can occur and the platelets break up to supply platelet factor 3. This is sufficient, with the plasma components Ac-globulin + calcium ions + platelet cofactor I (factor VIII, antihemophilic factor), to accelerate thrombin generation. This thrombin uses prothrombin as a substrate and the reaction specificity is governed by Ac-globulin. This is an autocatalytic feedback system (Figure 5). The precursor of autoprothrombin C found in the prothrombin molecule (autoprothrombin III) does not activate, or if it does, then only a very small percentage of the total potential becomes active.

The chemical events accelerated by surface contact and the platelets would be a threat to life if started within the blood vessels. A counterforce is generated by thrombin through the utilization of inhibitor source material of the plasma. The inhibitor neutralizes platelet cofactor I (factor VIII) activity, and for that reason platelet cofactor I is inactive in serum. The inactivation of platelet cofactor I would soon be noticed as retarded thrombin generation, because antithrombin would neutralize thrombin, and there would be no more thrombin remaining or any new thrombin generated. As a consequence prothrombin activation has to be continued in a newly created environment. This is possible by means of another regulatory function of thrombin.

By means of thrombin a new platelet cofactor activity develops while the above

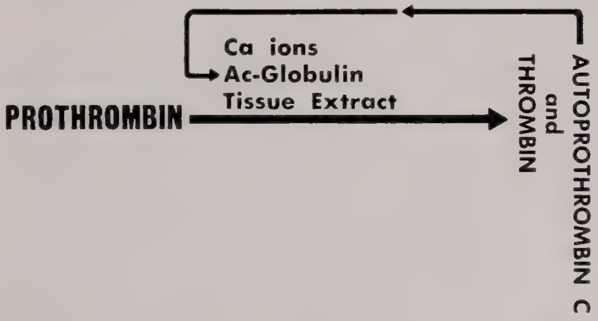

Fig. 7 — With the introduction of tissue extracts, active autoprothrombin C is produced as well as thrombin. Both enzymes then participate in the generation of thrombin activity. Ac-globulin is not essential for the generation of autoprothrombin C activity.

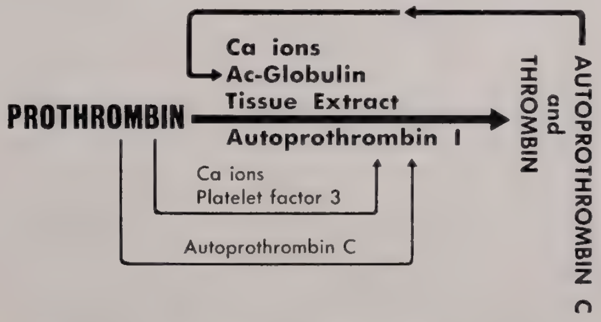

Fig. 8 — The effect of tissue extracts in the generation of thrombin activity is potentiated by the formation of autoprothrombin I. This activity develops in the presence of platelet factor 3 and also in the presence of autoprothrombin C.

described events are occurring (Figure 6). This is autoprothrombin II (factor IX or platelet cofactor II). Thrombin can form this derivative from prothrombin because the Ac-globulin does not completely enforce the reaction specificity which makes thrombin break prothrombin bonds at the site which gives thrombin. Some of the thrombin attacks at the site which is the primary target when Ac-globulin is not there at all. With cleavage of the prothrombin molecule at this point autoprothrombin II forms. In this laboratory autoprothrombin II was formerly called platelet cofactor II because it is really a substitute for platelet cofactor I. Notice that, except for the term autoprothrombin II or platelet cofactor I, the heavy lettering around the two arrows of Figure 6 is identical. This can be illustrated for explicit comparison as follows:

Ca ions	Ca ions
Platelet factor 3	Platelet factor 3
Ac-globulin (factor V)	Ac-globulin (factor V)
Platelet cofactor I (factor VIII)	Platelet cofactor II (factor IX)
Thrombin	Thrombin

For certain functions, platelet cofactor I (factor VIII) and platelet cofactor II (autoprothrombin II, factor IX) are interchangeable. The usefulness of each one depends upon the time sequence, and upon the exclusive capacity of platelet cofactor I to accept an inhibitor. Platelet cofactor II is found in serum and is not inactivated by the inhibitor for which platelet cofactor I is the receptor.

The chief reason for the slow clotting of the platelet-plasma system resides in the fact that autoprothrombin C remains in its precursor form: namely, autoprothrombin III. If any active autoprothrombin C forms, the quantity is small. Thrombin may be the only enzyme for prothrombin activation under the conditions where platelets + plasma are involved. It is not a very effective procoagulant when the coenzyme concentration (Ac-globulin) is no higher than found in plasma.

Tissue-platelet-plasma Activation Sequence

With Ac-globulin in plasma, thrombin generation can be accelerated with tissue extracts alone. Autoprothrombin C activity develops in large quantities due to the materials of tissue extracts (Figure 7). These materials are primarily lipoproteins and cathepsin. Ac-globulin is not necessary for the development of autoprothrombin C activity. The autoprothrombin C has its reaction specificity governed by Ac-globulin so that it tends mainly to convert prothrombin to thrombin. As stated previously, the same is true for thrombin. The two enzymes thus work synergistically. In test tubes the tissue-extract concentration and the Ac-globulin concentration can be set so high that the activation of prothrombin is rapid and almost exclusively to thrombin and autoprothrombin C (Figure 7), without the formation of any other prothrombin subunits.

In natural clotting, tissue extract and Ac-globulin are in limited concentration and clotting would be slow except that there is another mechanism for accelerating thrombin generation. This consists of producing autoprothrombin I. It occurs in two ways (Figure 8). In one way the reaction specificity of autoprothrombin C is not completely enforced and some of the autoprothrombin C converts prothrombin to autoprothrombin I_c (factor VII ?). The latter functions as an accelerator. Another pathway for autoprothrombin I generation develops, due to platelet factor 3. This lipoprotein called platelet factor 3 tends to induce the conversion of prothrombin to autoprothrombin I_p (factor VII ?), and this derivative is also an accelerator. Autoprothrombin I_c and autoprothrombin I_p can hardly be distinguished from each other on the basis of kinetic experiments. They are, however, easily seen to be different substances on the basis of solubility and stability characteristics. Neither is *necessary* for the development of autoprothrombin C activity or for the generation of thrombin activity. They are accelerators.

The full procoagulant power of blood and tissues is brought into force by the operation of several reactions (Figure 9). With its limitations Figure 9 can serve to reduce to a conceptual basis volumes of information gathered since the time of Alexander Schmidt. This way of viewing one of the most important reactions in biology is really an interpretation of the function of thrombin and autoprothrombin C in prothrombin activation. I know of no fact that is inconsistent with this analysis. Moreover, the reduction of plasma prothrombin concentration following vitamin K deficiency fully accounts for the decrease in the amount of autoprothrombin I, II, or III that can be derived from such plasma. One glance at the diagram of Figure 9 brings the realization that prothrombin activation can consist of many events at one time and that there is no sequence of events that can be insisted upon, except for one set of conditions. Work with purified clotting factors has, however, made it possible to study isolated reactions. From this information it is possible to construct such an integrated concept and claim validity for it. Short circuits, bypasses, and substitutions in such a system fully account for the infinite variations on the central theme of prothrombin activation. In rare cases even the prothrombin can be omitted as, for example, when snake venom clots fibrinogen directly.

Even though the summary of Figure 9 may seem complicated and is a description for only one set of conditions, it highlights fundamental principles and presents a concept which gives a student the foundation on which he can construct his working knowledge to deal with the individual variant. There are several outstanding facts.

Prothrombin is a molecular system or a multipotential molecule from which two enzymes, *thrombin* and *autoprothrombin C*, can be derived or from which other subunits can be obtained.

Whenever there are many prothrombin molecules, as under physiological conditions, a random prothrombin activation occurs which is representative of the particular conditions. One or another of the possible derivatives forms from one molecule. One or another of the possible derivatives forms from another molecule and so on to give the necessary impetus for getting an adequate amount of thrombin.

The antihemophilic factor (factor VIII, platelet cofactor I) first functions as a procoagulant and then as the receptor of an inhibitor which develops as a consequence of thrombin activity.

Autoprothrombin II is derived from prothrombin while the antihemophilic factor is still a procoagulant and being neutralized. It then serves as a relay to do the work begun by factor VIII.

Thrombin is the main activating enzyme in the platelet + plasma system; if autoprothrombin C is active the amounts are small.

Thrombin and autoprothrombin C are the activating enzymes in the platelet + plasma + tissue system.

The enzymes for prothrombin activation come from prothrombin itself and Ac-globulin functions as a coautocatalyst for these

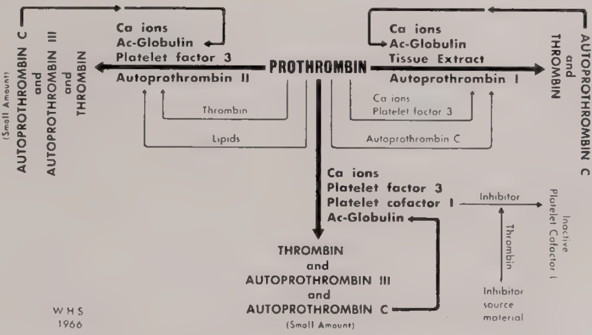
(Small Amount)
AUTOPROTHROMBIN C
and
AUTOPROTHROMBIN III
and
THROMBIN
Ca ions
Ac-Globulin
Platelet factor 3
Autoprothrombin II
PROTHROMBIN
Ca ions
Ac-Globulin
Tissue Extract
Autoprothrombin I
THROMBIN
and
AUTOPROTHROMBIN C
Thrombin
Lipids
Ca ions
Platelet factor 3
Autoprothrombin C
Ca ions
Platelet factor 3
Platelet cofactor I
Ac-Globulin
Inhibitor
Inactive Platelet Cofactor I
Thrombin
Inhibitor source material
THROMBIN
and
AUTOPROTHROMBIN III
and
AUTOPROTHROMBIN C
(Small Amount)
WHS
1966

Fig. 9 — A combination of text figures 5, 6, 7 and 8 to depict the full procoagulant power of plasma, platelets and tissues. These and many more reactions can occur simultaneously. The beginning or acceleration of thrombin generation can be due to contact which brings on platelet disintegration, and/or the liberation of tissue materials due to cellular injury. Also factor XII can be activated by surface contact.

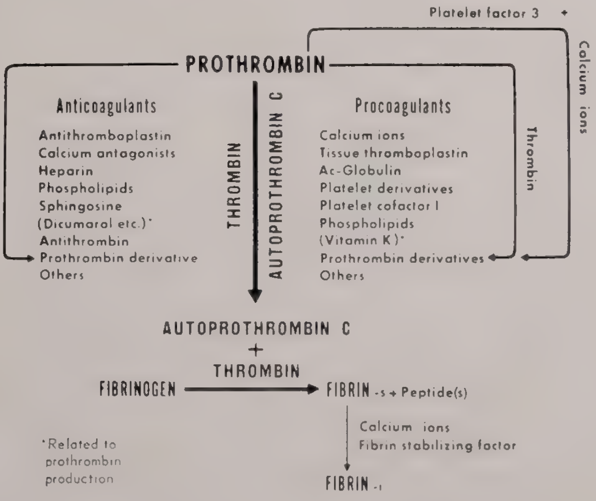
Platelet factor 3 +
Calcium ions
PROTHROMBIN
Anticoagulants
Antithromboplastin
Calcium antagonists
Heparin
Phospholipids
Sphingosine
(Dicumarol etc.)*
Antithrombin
Prothrombin derivative
Others
THROMBIN
AUTOPROTHROMBIN C
Procoagulants
Calcium ions
Tissue thromboplastin
Ac-Globulin
Platelet derivatives
Platelet cofactor I
Phospholipids
(Vitamin K)*
Prothrombin derivatives
Others
Thrombin
AUTOPROTHROMBIN C
+
THROMBIN
FIBRINOGEN
FIBRIN -s + Peptide(s)
Calcium ions
Fibrin stabilizing factor
FIBRIN -i
*Related to prothrombin production

Fig. 10 — General statement of prothrombin activation and fibrin formation which regards the procoagulant forces as being in balance with anticoagulant forces.

enzymes. Ac-globulin regulates the reaction specificity of the two enzymes.

Other prothrombin derivatives act as accelerators for the conversion of prothrombin to thrombin. The lipoproteins serve as accelerators of the interactions by their surface activity. They supply hydrophobic and hydrophilic forces for orientation in the enzyme activities. Calcium ions are needed in the coordination chemistry. All of what is outlined on Figure 9 can be bypassed by retaining only prothrombin and obtaining thrombin with an enzyme such as trypsin, or other suitable enzymes, or just a strong salt solution such as sodium citrate.

Serum

Serum can be regarded as a product of blood clotting and contains the spent products of those reactions. Some of the molecules concerned may remain in their original form, while other activities develop and get neutralized. Serum may contain autoprothrombin III from the platelet + plasma activation environment. Autoprothrombin C, autoprothrombin I. and thrombin are inactivated by antithrombin, and must be in serum combined with this inhibitor. The concentration of antithrombin in serum is less than that in plasma. Any autoprothrombin II activity which generates remains in serum. Ac-globulin is found in the serum of some species but is masked in others. Platelet cofactor I is associated with an inhibitor; the procoagulant power of tissue extracts tends to be neutralized and is not present in serum. There are, of course, platelet remnants, serotonin, and split products from fibrinogen, platelet factor 3 from platelets, and perhaps a similar substance from any hemolyzed red cells.

Polymerization of Fibrinogen

As soon as thrombin has accumulated in sufficient quantity and participates in the many reactions, it also finds fibrinogen as a substrate. As a result of this function, the fibrin clot is formed. Many of the details of this chemistry have been so well described that it is perhaps the best known example to illustrate the way in which structures are formed in biology.

The enzyme thrombin, which is an endopeptidase, removes at least one and not more than four peptides from the six long peptide chains of the fibrinogen molecule (M.W. = 330,000). Cleavage occurs at a particular arginyl-glycine peptide bond. The fibrin monomer which remains consists of practically all the original fibrinogen molecule, because the split-off peptides are small, the molecular weight of peptide A being 1,900 and that of peptide B 2,460. Several of such fibrin monomers associate end-to-end when peptide A is gone and form strands. Side-to-side polymerization occurs when peptide B is split off so that the strands enlarge their width. Then with branching also occurring, the fibrin network is built up. Electronmicrographs of such a network consist of alternate light and dark bands spaced in such a way that there is correlation with the original structure of the fibrinogen molecule.

The fibrin which is produced in the laboratory by the polymerization of purified fibrinogen in the presence of purified thrombin is soluble in 5 M urea solution, but the natural fibrin is not. The reason for this difference is that thrombin has a further function in the formation of a clot. Thrombin activates a protein in plasma usually called fibrin stabilizing factor or fibrinase (M.W. = 350,000) which becomes activated by thrombin. The fibrinase itself perhaps becomes a part of the clot, for it is not found in serum to any appreciable extent. For the function of fibrinase in clot stabilization, calcium ions, or a divalent substitute, are needed. The stable fibrin clot is thus an advanced consolidation of the slightly modified fibrinogen which is in plasma.

Summary Fibrin Formation

$$\text{Fibrinogen} \xrightarrow{\text{Thrombin}} \begin{matrix}\text{Fibrin}\\ \text{monomer}\end{matrix} + \begin{matrix}\text{2 Peptides A}\\ \text{2 Peptides B}\end{matrix} + \text{Carbohydrate}$$

$$\text{Fibrin monomer} \longrightarrow \text{Fibrin polymer}$$

$$\text{Fibrinase} \xrightarrow{\text{Thrombin}} \text{Active fibrinase}$$

$$\text{Fibrin polymer} \xrightarrow{\substack{\text{Ca ions}\\ \text{Active fibrinase}}} \text{Fibrin clot}$$

$$\text{Fibrin clot} \xrightarrow{\substack{\text{Platelets for}\\ \text{retraction}}} \text{Retracted clot} + \text{Serum}$$

For purposes of summarizing some of the basic enzymology in blood clotting, another diagram has been designed (Figure 10). It has many limitations which do not occur in Figure 9. The basic idea of prothrombin activation by autocatalysis is featured. The procoagulants, which are substances that promote thrombin generation, are listed. Likewise the anticoagulants, or substances which retard thrombin generation, are listed. Normally there exists a balance between procoagulant and anticoagulant forces.

Pathological Aspects

During the decades just passed, numerous irregularities in the blood-clotting mechanisms were discovered in hospitals and clinics. Ways and means were found to differentiate one abnormality from another, and in many instances effective therapeutic measures were employed. In other instances ways and means to provide help are still being sought for. Along with the clinical work, attempts were made to describe the nature of the underlying chemistry involved. A conspicuous error permeated the working rationale: it was assumed that a defined deficiency which differs from another is due to lack of a previously unknown clotting factor. Then the hypothetical factors were given numbers by the International Committee on the Nomenclature of Blood Clotting Factors. The next task is to differentiate between what was created by committee work and what was created by work in the laboratory. Already the biochemical aspects are outlined as described above and in other papers.[1-7] Since this represents basic chemistry, it subsumes the hypothesis advanced at the clinical level of observation, as stated recently.[8-12]

The following notes on pathological manifestations highlight most of the main problems. Irregularities in clotting can occur when fibrinogen is absent. Lack of the fibrin stabilizing factor is associated with an abnormal fibrin network. If there is a deficiency of vitamin K due to lack in the diet or faulty absorption, or if liver function is abnormal, very little prothrombin synthesis can occur in the liver, and prothrombin derivatives cannot be formed. Evidently factor VII, IX, and X deficiency are due to an abnormal prothrombin molecule. In parahemophilia there is a reduced plasma Ac-globulin concentration. In von Willebrand's disease there is a low concentration of platelet cofactor I (factor VIII), and also of a substance needed for hemostasis. In hemophilia A there is excess of an inhibitor, and not a lack of platelet cofactor I as was generally thought previously. Besides a reduction in platelet numbers there are conditions in which platelet factor 3 is absent or not released for its proper function. Factor XII deficiency apparently is not associated with a bleeding tendency. The severe complications in placenta abruptio bring changes in Ac-globulin, fibrinogen, factor VIII, and to a lesser extent in prothrombin. The clotting mechanisms are brought into play by bacterial endotoxins, trypsin, and snake venoms. In thrombosis, as a result of many conditions still to be described, fibrin deposits are involved.

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6-12 May be secured from the author or the reprints.

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Medicine and Religion

Schweitzer on the Paranoia of Jesus

Albert Schweitzer is remembered as theologian and physician. Yet it is seldom realized the importance his medical studies had for his theological research at one point. This was in his M.D. thesis, *The Psychiatric Study of Jesus: Exposition and Criticism,* 1913. Schweitzer was dealing with a question of importance to both physician and theologian. What is the relationship between religious faith and mental illness? If religious experience, especially that of great religious leaders, derives partially from psychopathology, can the ethic and religion based on such experiences be an appropriate guide for life? This question was cast in its most controversial form when focused on the person of Jesus. This had been done early in this century by the work of three psychiatrists: George Lomer (who wrote under the pseudonym de Loosten), William Hirsch and Charles Binet-Sangle. These writers were influenced by the work of Emil Kraeplin on paranoia, which provided the theoretical basis for the study of Jesus' life and thought as an example of psychopathology. While they differed as to the etiology and progress of the disease, they all concluded that Jesus suffered from severe paranoia characterized by visual and auditory hallucinations; that the disease was marked by progressive deterioration in which Jesus increasingly identified himself as a divine being who would bring in the Kingdom of God.

To understand such an interpretation of Jesus and Schweitzer's response to it, it is necessary to recall two intellectual developments of the nineteenth century: First, the rise of an undogmatic, historical study of Jesus and the origins of Christianity; Second, the development of psychoanalytic psychology. Paradoxically, it was the new historical research that raised in heightened form the question of Jesus' mental state. Since the work of D. F. Strauss, 1835, historians had recognized the importance for Jesus of the apocalyptic ideas drawn from Judaism which focused on the imminent end of the world. Schweitzer in his earlier book, *The Quest for the Historical Jesus,* had shown that Jesus thought of himself as a central figure in the drama of the end times. So it was not surprising that many looked to Schweitzer to absolve Jesus of the paranoia which had been assigned to Him by the psychiatric interpreters.

Schweitzer worked for a year on his brief monograph relating to the new literature on paranoia as it pertains to the complexities of the New Testament. He uncovered two underlying fallacies in the work of de Loosten, Hirsch and Binet-Sangle. First, their historical analysis was inaccurate: they treated the Gospels as if they were verbatim reports of the sayings of Jesus. Actually, the Gospels represent an expansion upon the sayings of Jesus. The claim of Hirsch that Jesus' preaching culminates in one word:

Continued

"I," represents an uncritical reading of the markedly unhistorical Gospel of John. It is an assertion that will not be supported by comparison with the Synoptic Gospels. Second, these interpreters had failed to understand Jesus' relation to the religious world-view of his contemporaries. Jesus' ministry was not shaped out of a set of delusions he developed himself but from the context of contemporary religion. The expectation of the end of the world, demonic and angelic intervention in human affairs, and the coming of messianic deliverers were all part of the then normative conception of reality. Jesus' presentation of himself as a key figure in the drama of the end times has a rationality in light of its contemporary world-view, which it lacks in our own. The participation of a man of the first century in the religious ideas of his time is no proof of his insanity no matter how bizarre the ideas seem to modern men. While Schweitzer demonstrated the work of the psychiatric interpreters to be vitiated by historical misunderstanding, he also recognized they had raised an important issue. Can a man of the past, emerging within a conception of reality foreign to our own, provide a guide in religion and ethics? Specifically, can Jesus, the apocalyptic visionary of the first century, guide a man of the twentieth? His answer was, "Yes." Paradoxically, Schweitzer believed the abiding importance of Jesus derived from his coming to us from outside our culture. The apocalyptic vision of Jesus is important because it forces men to look beyond the limitations of their own time and place to seek new moral alternatives. The vision of a world under judgment, of a world nearing its end, reminds men of the smallness of their life goals and values. It is a vision that calls the religiously and ethically serious man to seek ever new means for service. In this light Schweitzer redirected his own life, so he could say, "I came to Africa in obedience to the call of Jesus."

Prof. Donald G. Dawe, B.S. (Wayne State, '49), B.D., Th.D.
Macalester College, St. Paul, Minnesota

On Gathering Simples

That the plucking of herbs and digging up of roots was a process very apt to be attended by magical procedure we find abundant evidence in Pliny's Natural History. A common instruction is to pick the plant with the thumb and fourth finger of the left hand; or the right hand should be stretched covertly after the fashion of a pickpocket through the left sleeve in order to pluck the plant. Sometimes one faces east in plucking herbs; sometimes, west; again one is careful not to face the wind. Sometimes the gatherer must not glance behind him. Sometimes he must fast before he takes the plant from the ground; again he must observe a state of chastity. Sometimes he should be barefoot and clothed in white; again he should remove every stitch of clothing. Often the plant must not touch the ground again after it is picked, presumably from a fear that its virtue would run off like an electric current.*

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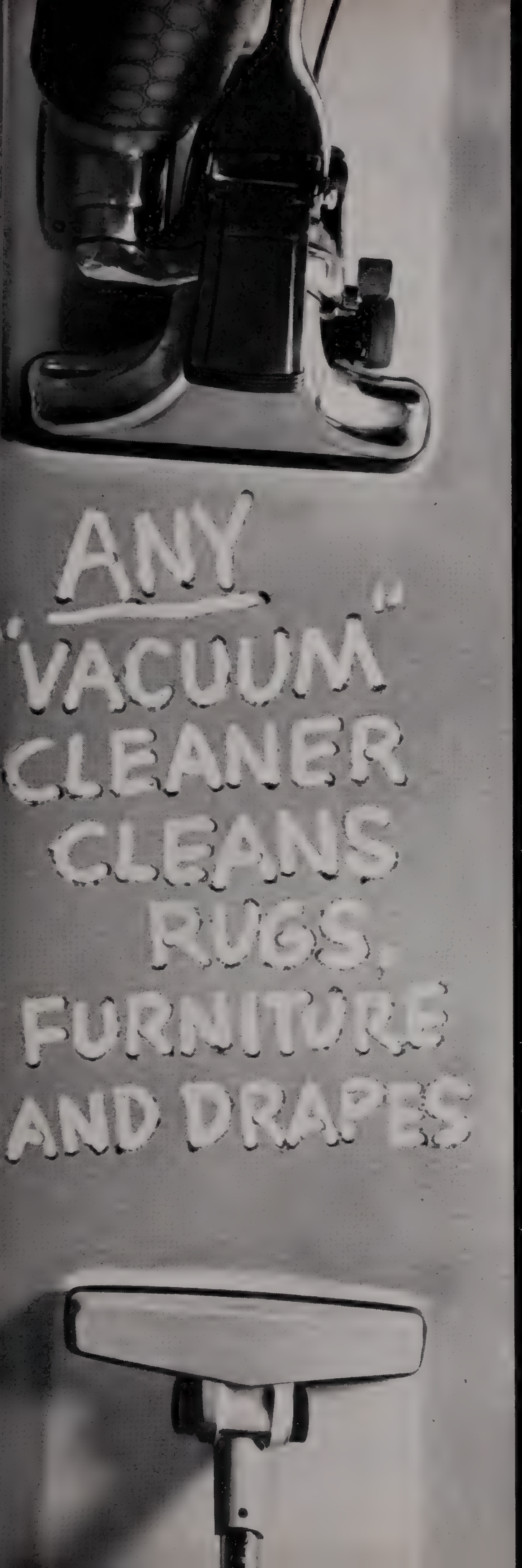
*Thorndike, Lynn: A History of Magic and Experimental Science, Vol. 1, p. 78. The MacMillan Company, New York, 1923.

Civility is a charm that attracts the love of all men; and too much is better than to show too little. — Bp. Horne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3 Now turn the machine over to any one witnessing the demonstration, and have her start the machine and apply the nozzle to any place where there is obvious dirt and dust. Keep the machine operating for a full minute.

See the proof with the FILTER QUEEN *"clean handkerchief" test*

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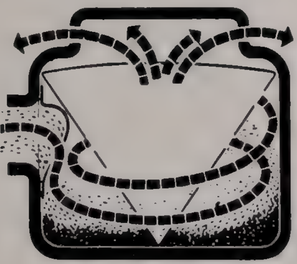

Why not ask your local FILTER QUEEN Distributor to make the dramatic handkerchief test (pictured at left) in your hospital? There is no better way to prove the improvement in cleaning ability between a FILTER QUEEN SANITATION SYSTEM and any type of vacuum cleaner. (You'll find your distributor listed in the Yellow Pages; or write Health-Mor, Inc. direct).

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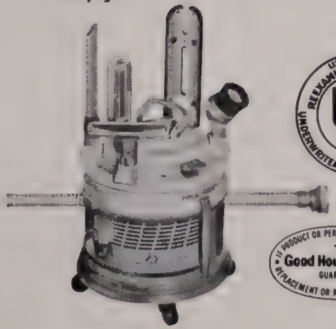
"One of the most pleasing features of the machine is its quietness. We can even clean in the rooms while occupied by the patients, and many have commented on how pleasant it is not to be disturbed by noisy, old-fashioned vacuum cleaners anymore."

"The air exhaust at the top of the unit is a wonderful feature, and the Sanitary Filter Cone is certainly our answer for working in closely confined patient areas."

"We thought we had a clean hospital and a fairly good method of achieving acceptable sanitation, but this little machine made us revise our thinking and our methods."

"A quiet motor which possesses excellent cleaning power and the convenience of having to clean out the cleaning compartment only once a month, has proved very advantageous. One of the most important points . . . is that there is no bag to empty."



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History of Medicine

Avicenna, The Prince of Physicians[*]

Part II

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The Humors

Avicenna's concept of the humors was essentially Galen's. Healthy humor was that moist substance which replaced the loss which the body substance underwent. The residue, or superfluity, was called unhealthy humor. There were four body fluids or humors, namely: sanguineous or hot-moist; serous or cold-moist; bilious or hot-dry; and atrabilious or cold-dry. These, in turn, could be normal or abnormal in varying degrees. Avicenna felt that Galen was wrong in holding all the humors but blood as superfluities; but the reasoning for his disagreement with Galen was purely dialectical; e. g., if the serous humor did not nourish the brain, the brain would not be soft.

His division of the bodily members included the bone, cartilage, nerves, tendons, ligaments, arteries, membranes and flesh. Each member in turn possessed at least the vegetative faculty, i.e., the powers of attraction, assimilation, expulsion and growth. This type of dialectical reasoning and classification formed the substructure of his medical theory as well as that of the European schoolmen after him. Suffice it to say that his dialectical approach quite naturally possessed the weakness of becoming progressively more detached from actual observation.

It is often difficult to ascertain in such authors as Avicenna what was the result of clinical observation and what the result of purely abstract reasoning, particularly since any clinical observations were consistently analyzed by the traditional facultative and humoral anatomy and pathology.

Metabolism

Avicenna, as Galen, Aristotle and others before him, always began his analysis of the human body with the vegetative faculty or what we might today call the process of nutrition or, more cautiously, 'metabolism.' He regarded this as primarily a four-stage process of breaking down food into chyle by means of the heat and the excessive moisture of the surrounding visceral organs.

The Nutriment

The chyle passed into the intestine, then was drawn off by the mesenteric vessels into the portal vein, thence into the liver, which manufactured the blood and carried the nutriment into the superior vena cava. At the same time, excessive moisture from the liver along with blood 'fat' and some blood passed into the kidneys. The blood manufactured by the liver was conveyed along into smaller and smaller cavities until it 'sweated' out, i.e., until it reached each portion of every member including the skin. While in the veins, the nutriment underwent a third digestion and, upon reaching a member, underwent a fourth digestion during assimilation.

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[*] Avicenna (980-1036 A.D.) or Abú 'Ali Husayn ibn 'Addullah ibn Sina; also called the "Chief Master" or "Second Master," i.e. after Aristotle. Presented before the Society of Medical History of Chicago, January 23, 1963. See Part I Minnesota Med 48:1567, 1965.

[**] History of Medicine Division National Library of Medicine.

Continued

The Waste Products

Waste products from the first digestion passed out through the intestines; those from the second digestion in the liver passed out chiefly by the urine, but also by the spleen and gall bladder. The waste from the third and fourth digestions passed out by perspiration, sordes, nostrils, ears, invisible pores, or through suppurations.

The Principal Organs

The principal organs were held to be the brain, heart, liver, and reproductive 'gland.' The afferent organs were the sense organs, lungs, stomach, intestines, veins, and constituents of humors. The efferent organs were the nerves, arteries, gallbladder, spleen, kidneys, ducts and genital adnexa. The elementary tissues included the bones, cartilages, ligaments, muscles, fasciae, tendons, membranes, flesh, fat and intestinal tract. The members, in Avicenna's system, could also be classified according to their origin, e. g., from the blood or sperm. He recognized the existence of tissue or fiber layers in the blood vessels, intestines and muscles. He seemed to recognize the existence of blood in the arteries but thought that their primary function was to carry the 'breath.' Strong members expelled their waste matter into weaker members, e. g., the brain to the tissues behind the ears.

Unfortunately, his anatomical knowledge did not exhibit any details that could have come from animal dissection, much less postmortems. In this respect, he was inferior to Galen, whose culture as least permitted vivisection of a pig. The Islamic culture, as well as the Judaic and the Christian cultures until the thirteenth century, did not permit human dissections.

The Stages of Disease

In his pathology Avicenna resorted to logical distinctions of causes, symptoms, signs, etc. In other words, he employed the arguments of logical causality to differentiate cause from symptom, symptom from sign, without bothering to discuss the actual disease phenomena. He recognized four stages of disease: onset, increment, acme and decline. Diseases could be named according to the member affected, the chief symptom, the originating humor, the resemblance to animals, the first historical example, or according to the essential nature of the disease (e. g., fever).

Epidemiology

In his discussion of epidemiology, he included, under transmission by infection, the notion that eye diseases could be transmitted by a gaze. He also recognized hereditary, racial, endemic, and atmospheric transmission. His descriptions of the role of the atmosphere, seasons and climate were traditional from Hippocrates. His discussion of how these factors influenced health was a restatement of the theory of the interaction of the four elemental qualities of hot, cold, wet, dry, and the correlative humors and temperaments.

His notions of dietetics were likewise a restatement of traditional views found in Galen and Paul of Aegina, the seventh century Byzantine compiler. Interestingly, he included a lengthy section on water in which he recommended purification by boiling, sublimation and distillation. He noted that, excluding climatological factors affecting health, the body could also be influenced by external agents which are not injurious *per se.* For example, the body could absorb the primary quality of an application such as a plaster through the pores, or there could be a combination of external and internal qualitative changes. His concept of balneology continued this fundamental notion of the role of external agents producing qualitative changes by altering the balance of the four elemental qualities.

Pain

In his concept of pain, he professed to disagree with Galen in attributing loss of continuity to be a primary cause of pain. He felt that pain was rather a transmutation of the temperament of the affected part. In this connection, he listed 15 different types of pain. The causes he assigned for these pains were again consistent with his four elemental qualities, with the consequence that alleviation of pain was by counteraction.

Signs and Symptoms

His discussion of diagnosis by signs and symptoms was also consistent with the four-qualities theory. His main contribution was perhaps a greater emphasis on tabulation. In our age of laboratory analysis, x-rays, and other techniques to determine the nature of a patient's health or illness, it is difficult to appreciate the enormous store which Avicenna and those following him placed on feeling the pulse, on uroscopy, and on fecal examination. While such examinations were employed at least as far back as Galen and even basically noted in the Hippocratic writings, by Avicenna's time they had become codified into a 'science,' requiring lengthy tabulations of tactile (pulse), visual and odor (urine and fecal) qualities. The urine flask being examined by the doctor became the standard art symbolism of Avicenna's medieval successors.

The Pulse

Avicenna listed 11 basic types of irregular pulse. These were considered the simple pulses and could, in turn, again be subdivided into compounds; but he felt the subdivisions were too numerous to list. There were basically three contentive factors in producing the pulse: the vital power of the heart, arterial elasticity and arterial resistance. These in turn could be subdivided into essential and nonessential, and again redivided. Pulse could also be related to age, temperature, season, emotions, habits, temperaments, and locations.

Uroscopy

As did pulse lore, so did uroscopy in Avicenna reach a high degree of tabulation. The basic philosophy of uroscopy was primarily to determine liver function, i.e., the functioning of the liver as a second agent in metabolism and hematopoiesis. Secondarily, the examination was to determine the state of the urinary passages and blood vessels. The urine was examined for quantity, odor, color, foam, texture, clearness, and sediment; we cannot profess to evaluate the number of visual qualities which Avicenna listed. Suffice it to say, however, that he believed such qualities could be correlated with the four elemental qualities of the humors as they

Continued

are expressed in his pathology. He professed to be able to differentiate, among other things, pregnancy, sex and age, cerebral disorders, jaundice, and human and animal urine. Except for sterilizing the bottle, the method of collection was about as precise as today. There was also a prescribed regimen to be followed before giving the specimen, as well as a precise time for collecting it.

Fecal Examination

Fecal discharges were examined for quantity, consistency, color, form or shape, and time occupied in passage. Findings were also correlated in tabular form according to the humoral pathology.

In his total view of the life process, he repeated in condensed form various traditional notions, such as death being the extinguishing of the innate heat, and the male sperm being the formative agent while the female provided the matter for generation.

The Specialties

In his concept of nutrition, following traditional lines, he began with pediatrics and continued the discussion through geriatrics. These topics were also treated according to the humoral concept of establishing the right temperament for the right age. In his pediatrics, he covered teething, convulsions, night terrors, brain inflammations, ear-nose-and-throat disorders, respiratory and digestive disturbances, hernia, worms, skin disorders and fevers. In discussing regimen from infancy to adolescence, he insisted that the one great principle was the inculcation of emotional control. This was to be accomplished by removing all emotional irritants so that the mind could grow free from anxiety.

In discussing adult regimen and exercise, he reflected to a great extent what must have been the high cultural level of his times by his constant references to the public bath houses and varieties of wines. In this connection, he also prescribed anti-inebriants and restoratives. He recognized hepatic and nerve damage from excessive drinking. He also discussed anesthesia, including wine, opium, nerve depressants (aloes), and narcotics (mandragora and darnel).

Therapeutic Measures

His therapeutic measures included purgatives, emetics, cupping, venesection, leeches, liniments, and minor surgery. Consistent with his general medical theory, he envisioned therapy as being the physician's attempt to restore the balance in the temperaments. He employed a logical scheme for treating by opposites, e. g., plethora by depletion. These techniques were accompanied by detailed rules.

Purgatives

Before administering a purgative, the physician had first to determine which of the humors were at fault, how to prepare the body for the purge, and who should or should not be given purges. An example of the latter was the notion that people who lisp were liable to gastrointestinal catarrh and therefore could not stand strong purges. Avicenna probably also had occasion to treat impacted feces, since he pointed out the danger of using purges in their presence, and recommended instead enemas and emollient broths. As with purgatives, Avicenna also gave detailed rules for emetics, much of which appears to have been taken from Paul of Aegina and Rhazes.

Venesection

Venesection was to be resorted to in order to remove excessive humors present in the blood vessels, and was to be resorted to either when the blood was so superabundant that a disease was about to develop or when the disease was already present. If the disease was already present, bloodletting could be resorted to only after the acme of the disease had been passed. Cupping was envisioned as a method of cleansing a particular area of the skin more effectively than bloodletting by drawing off the more rarefied rather than the more viscid blood. It was used to draw out deep inflammations, to divert an inflammation to a neighboring part, to restore a member to its proper position, or to allay pain. The points of application and the corresponding therapeutic uses were also tabulated.

Leeching

Leeches were used to withdraw blood deeper down than that which could be obtained by wet cupping. Inflammatory swellings were treated by astringents, resolvents, refrigerants, venesections or purgatives, depending on their humoral cause. Cautery was recommended for gangrenous ulcers, preventing the spread of a destructive lesion, rectifying the cold temperament of a member, breaking up putrefactive matters imprisoned in a tissue, or controlling hemorrhage.

Priority of therapeutic measures was guided by three principles:

(1) When one malady had to be cured before the other could be relieved.

(2) When maladies were related as cause and effect.

(3) When it was absolutely essential to deal with one of the maladies, even though the other may not have been relieved by the treatment.

Psychology

Avicenna, as other Islamic and European medieval writers following the Aristotelian tradition, did not of course use the term ‘psychology’ but rather the term ‘soul.’ The term ‘soul,’ however, did not have a purely religious meaning, nor was it merely some ethereal principle leaving us at death. Rather Avicenna’s concern with ‘soul’ represented a serious exercise in reasoning to determine the differences between a simple organism and a human organism. As others in this tradition, he attempted to differentiate levels of ‘soul’ by means of vegetative, sentient, and reasoning faculties. He further wanted to differentiate between creatures with a reasoning faculty (man) and creatures who must, by the laws of the Aristotelian logical causality, exist prior in some manner to man. In this respect, unlike Averrhoes, he preserved the religious orthodoxy of his psychology by insisting on the individuation of the human soul apart from the heavenly ‘active intellect’ or ‘world soul.’ Moreover, he showed much concern with what we would term ‘physiological psychology.’ This concern was expressed by dwelling on the ‘motive’ aspects of the soul, i.e., the emotions, the vital breath, and why the emotions were expressed by particular bodily aspects. That his reasoning was completely dominated by his Aristotelian logic and the humoral theory does not negate

Continued

the fact that it was this emphasis or interest that was later to be picked up by Vives, Descartes, and others until it found expression in the 'dynamics' and 'associationism' of modern psychology.

References

1. Avicenna: Opera Philosophica, Venice, 1508 Facsimile, Louvain, 1961.
2-11 May be secured from the author or the reprints.

History of Medicine in Wright County*

In 1879 **Dr. Neil Downey** of Minneapolis announced that he would come to give dental services for five days. He offered to take on any dental work. It seems he did not continue this for very long. In February, 1880, **Dr. E. Pentecost**, a dentist of Willmar, Kandiyohi County, offered his services in Delano — "prepared to practice dentistry in all its branches."

In the summer of 1881 **Dr. Jewett** of Minneapolis promised regular visits to Delano, and in the same year **Dr. S. C. Carter's** name appears. Dr. Carter was a heavy advertiser and remained much longer than practically any of those mentioned so far. He was, no doubt, a resident dentist in the early 1880s. In 1883 he resided in Howard Lake and visited Delano on the third Wednesday and Thursday of each month, practicing at Young's Hotel. From 1887 on, or even earlier, he had his office in Minneapolis, coming for two days to Maple Plain, for the same period to Delano and Waverly and for only one day to Montrose. The first three days of each week he reserved for his Minneapolis clientele. In 1888 he allocated two days to Delano, one to Montrose and three to Watertown, Carver County. Late in 1889 his card read "Dr. and Mrs. Carter, dentists Minneapolis."

In 1882 several dentists tried their luck in Wright County. In April **Dr. R. R. Todd** opened dental rooms in Hank Ball's Gallery in Delano in order to practice a week or so at a time in that town and in Waverly, but also in Watertown, Carver County. He promised painless extractions and "prices as low as the lowest." In August **Dr. L. M. V. Russell** announced his plans to come to Buffalo and Delano. In the latter town he would practice the last week of every month. In October **Dr. Holden** announced his services in Monticello.

In August 1883 **Dr. N. Ellis and Son** of St. Paul announced their plans of practicing in Delano and Rockford, perhaps as long as a week at a time. "Teeth extracted without the least pain or injury by the use of vitalized air. Artificial teeth from one to an entire set; a perfect fit is given in every case or no pay." In Delano they used first the Danforth House and later the Centennial Hotel. Soon they included Monticello in their circuit.

From 1884 to the end of the decade **Dr. W. Niven** of the firm **Morgan and Niven**, Minneapolis, advertised as "Painless Dentist" and "Teeth extracted by use of Nitrous Oxide or Ether. Special attention to preservation of natural teeth with gold, silver, and cement fillings. Intends to come periodically." He practiced in Rockford and Buffalo and also in Watertown, Carver County, and stayed at times as long as a week. In Delano he usually stayed at the Danforth House. Early in 1885 a **Dr. McKeel** announced his intentions of regular visits to Delano.

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*See Minnesota Med 48:1568, 1965.

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Medical Economics

What's Doing in Washington...

Health Legislation Record Set by 89th Congress

More and farther-reaching health legislation was enacted into law in 1965 than ever was enacted by a previous Congress.

Medicare and the heart disease, cancer and stroke programs topped the list of such legislation enacted into law, but there also were other important new health programs authorized. Several existing ones were expanded.

Approved health legislation included:

—A $787 million aid program for medical, pharmaceutical and other health schools. It authorized for the first time federal scholarships for students and operating funds for medical schools.

—A $105 million program of aid for medical libraries.

—A $250 million, three-year extension of grants for construction of health research facilities.

—Authorization of strict federal controls on manufacture and sale of barbiturates and amphetamines.

—Requirement that cigarette packages, beginning January 1, 1966, carry a health hazard warning.

—Extension of the vaccination program and expansion of it to include measles.

—Annual appropriation of a record $1.2 billion for the National Institutes of Health.

—Three new assistant secretaries of Health, Education and Welfare — one for health affairs.

—A four-year $92.5 million program of aid to municipalities for construction of garbage disposal plants and research in the field.

—Greater federal powers in the water pollution field, and $300 million to help communities build sewage plants.

—New federal powers to control air pollution, including requirement that new autos have devices to reduce exhaust fumes.

—Expansion of the federal vocational rehabilitation program, including $300 million in grants for building and initial staffing of rehabilitation facilities and workshops.

—A four-year $173 million program for initial staffing of community health centers.

—An administration on aging in the Health, Education and Welfare Department.

—Appropriation of $157 million for "Project Headstart" — nursery school training and medical examinations of pre-grammar school children from low-income families.

—A $69 million hospital program for the Appalachian area.

—Automatic rank of lieutenant general or

Continued

vice admiral for surgeons general of the army, navy, and air force.

—Extension for three years of the program of grants for health services for domestic migrant agricultural workers.

—A one-year extension of program of grants for general health aid and for community health services.

Federal Agencies Take Antihistamine-Patent Medicine Stand

Federal agencies relaxed regulations for the sale of Ipecac, ordered warning labels on certain antihistamines and cracked down on two patent medicines.

The Food and Drug Administration decided that ready availability of Ipecac as a poison remedy outweighed the dangers of possible misuse and placed it back on the list of drugs for sale over the counter without a prescription.

Since Ipecac was placed on a prescription-only basis in January, 1964, the American Medical Association, the American Academy of Pediatrics and the Association of Poison Control Centers had urged that the vomit-inducing drug be returned to its former status.

Under the new FDA ruling, FDA's Bureau of Medicine told the pediatrics group in Chicago that FDA decided it would be in the public interest to permit Ipecac to be sold over the counter in one-fluid-ounce bottles with special warnings on dangers of its misuse.

The FDA also ruled that in the future antihistamines containing meclizine, cyclizine and chloro-cyclizine must bear labels warning against use by pregnant women without medical advice. However, they were left on the over-the-counter list. The FDA said massive doses of these drugs in test animals had produced congenital abnormalities, but there had been no evidence they have caused abnormalities in human babies.

Chas. Pfizer & Co., Inc., one of the companies that manufacture such antihistamines, protested the decision as not being "in accordance with the medical facts."

A House Government Operations Subcommittee headed by Rep. H. L. Fountain (D., N. C.) recently had criticized the FDA for its handling of these antihistamines, contending that stronger warnings were needed and indicating that they should be prescription items.

The FDA ordered a halt to the sale of Alergimist "A" and "B," widely advertised as "cures" for hayfever, bronchial asthma, migraine headaches and allergic dermatitis.

The product has been actively promoted through newspaper, radio and television ads without having been passed by the agency as either safe or effective. The product, sold without a prescription, was being distributed by the Brunson Corporation of Miami Springs, Florida. FDA said the same concern previously distributed Allergimist (with two "l"s) until an injunction in September, 1964, was obtained against its interstate shipment.

The Federal Trade Commission ordered the J. B. Williams Co. of New York City to stop allegedly misrepresenting the effectiveness of "Geritol" liquid and tablets. The Commission ruled that Geritol television commercials and newspaper advertisements falsely represent that all cases of tiredness, loss of strength, run-down feeling, nervousness and irritability indicate a deficiency of iron and that the common, effective remedy for these symptoms is Geritol.

Geritol is not beneficial except in the small minority of persons whose tiredness symptoms are caused by a deficiency of iron or one or more of the vitamins contained in the preparation, the FTC said.

A sufficient and sure method of civilization is the influence of good women.

— Emerson

Medical Education

14 New Medical Schools Seen Within Five Years

Fourteen new medical schools are expected to be in operation in the United States by 1970.

These will bring to 101 the nation's total of schools of medicine and mark an "era of major expansion" in American medical education, according to the November 15th issue of the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION.

"Of obvious and immediate importance is the fact that 800 to 1,000 new positions will be available to qualified medical applicants," the Journal said. "This will help to meet the urgent national need for more physicians."

In addition to these 14 firm commitments to build schools, at least ten other institutions "seem to be reasonably good possibilities to follow through with the development of a new (medical) school," the Journal said.

The new medical schools are but one of the indicators that American medical education is expanding.

The 65th annual report on medical education by the AMA's Council on Education appeared in the November 15th issue of the Journal. The report contains data which mark continuing gains in graduate medical education, continuing medical education, educational programs in areas allied to medicine and programs of government agencies pertinent to medical education.

All of the new medical schools will introduce modifications of the standard medical curriculum. This should lead to "some very interesting experiments in medical education," said the Journal. The new schools also will be competing for faculty with existing schools.

"This will certainly aggravate an existing manpower problem, but it will also open up new opportunities for leadership to young, vigorous medical scientists," the Journal said.

Over the past 20 years, the number of medical schools has increased steadily from 77 schools in 1945 to 88 in 1965. The next five years, however, will mark the period of greatest expansion. Eight of the 14 schools being planned will provide full four-year programs leading to the M.D. degree. The other six are envisioned as two-year schools of the basic medical sciences.

"However, three or four of the latter may well progress directly to four-year programs after they have become firmly established," the Journal said.

The four year schools: The University of Arizona College of Medicine, Tucson; University of California School of Medicine, San Diego; University of Connecticut School of Medicine, Farmington; Milton S. Hershey Center, Pennsylvania State University, Hershey; Mt. Sinai School of Medicine, New York City; South Texas Medical School, University of Texas, San Antonio; University of Massachusetts and Toledo State College of Medicine, Toledo, Ohio.

The two-year schools: Brown University Program in Medical Science, Providence, Rhode Island; University of Hawaii Medical School, Honolulu; Michigan State University College of Human Medicine, East Lansing; Rutgers University Medical School, New Brunswick, New Jersey; University of California at Davis and the University of New Mexico School of Medicine, Albuquerque.

The University of New Mexico accepted

Continued

its first class in September 1964. As a developing two-year school, it becomes eligible for full accreditation when its first class nears the end of the sophomore year.

Rutgers expects to admit a small class in September 1966. Arizona, Brown, Hawaii, Hershey, Michigan State and South Texas are planning to begin in 1967. All of the 14 schools should be in operation by 1969 or 1970.

Postgraduate Medical Education Expanding

Most physicians continue to study medicine long after entering practice, and the number of postgraduate medical courses available to them has increased nearly 50 per cent in the past five years.

This year, 1,641 courses are being offered in 40 states and the District of Columbia, reports the November 15th JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION which contains the 65th annual report on medical education by the AMA's Council on Education. The number of physicians registered in these courses may be over 150,000.

Attending courses, however, is only one of the ways a doctor continues his education. Most physicians rank their continued reading of medical literature as one of their most important sources of new knowledge. They also continue their education through professional contacts with other physicians and through hospital staff meetings and national, state and local medical society meetings.

Formal postgraduate courses, however, are becoming increasingly important. Medical schools continue to be the major sponsors, but courses also are offered or co-sponsored by medical societies, voluntary health agencies, hospitals and governmental health agencies.

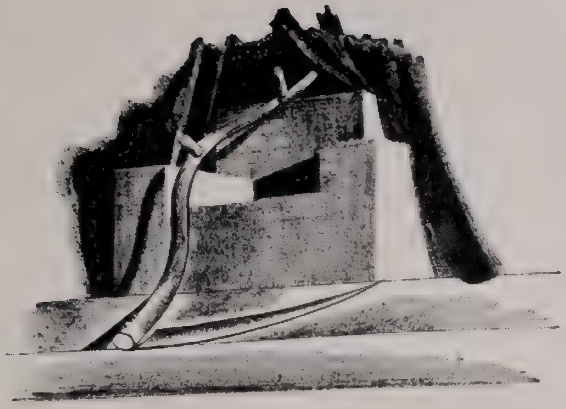
The most popular subject when doctors return to class? Psychiatry, by a wide margin. Courses in general medicine come next. Special subject areas such as pathology, surgery, ophthalmology, obstetrics-gynecology and cardiovascular disease also are popular.

Figures are not now available on the total number of physicians attending continuing education courses. Partial figures indicate that there has been a marked increase since last year.

During the 1964-65 academic year, there were 88,845 registrations at courses sponsored by medical schools. Medical schools sponsor about half the courses. If attendance at other courses was similar, the total registration last year must have exceeded 150,000, the report said.

The Nasturtium

Albertus Magnus (1193-1280), expatiating on the therapeutic virtues of the nasturtium, said: "It possesses acidity, is hot and dry, acts as a gentle purgative and laxative, and dries up the putridity of an empty belly. Used as a potion and liniment, it keeps the hair from falling out. Combined with salt and water, it helps abscesses and carbuncles, and mixed with honey, it eradicates Persian Fire and is good for all softening of the muscles. It purifies the lungs and relieves asthma by its sharp, cutting qualities. It warms the stomach and liver and cures enlarged spleen, but its disturbing quality is bad for the stomach. It is good for venomous bites, and if carefully prepared, works many other effects."



In Memoriam

Death will be what health is to the sick man; what home is to the exile; what the loved one given back is to the bereaved. — Fuller

ROSCOE C. HUNT, M.D.

Dr. Roscoe C. Hunt, 82, life-long Fairmont physician and surgeon, died November 13, at a nursing home at Rhinelander, Wisconsin. He was born in Fairmont and received his degree of medicine from the Harvard Medical College.

He was a member of the American College of Surgeons, the Blue Earth Valley Medical Society, and the American Medical Association. Dr. Hunt was a 50 Club and life member of the Minnesota State Medical Association. It was Dr. Hunt and his father, Dr. F. N. Hunt, who founded the Hunt Clinic which now is the Lakeside Clinic in Fairmont.

He is survived by his wife, two daughters, and two sons, Dr. Robert Hunt of Portland, Oregon, and Dr. William Hunt of Danville, Pa.

HAROLD H. JOFFE, M.D.

Dr. Harold H. Joffe, 54, Virginia pathologist, died September 30, en route from his home to the hospital. He was born in Chicago and was a graduate of the University of Illinois Medical School.

He was a member of the American Clinical Pathologists, College of American Pathologists, Minnesota Society of Clinical Pathologists, American Medical Association, Minnesota Medical Association, Range Medical Society, Virginia Chamber of Commerce health committee, and the Masonic Lodge.

He is survived by his wife, a daughter and two sons.

ALMER M. AANES, M.D.

Dr. Almer M. Aanes, 79, former Goodhue county health officer and a physician for more than fifty years, died November 28. He was born in Clermont, Iowa, and obtained his medical degree at the University of Iowa.

For twenty-five years, Dr. Aanes was a surgeon for the Milwaukee Railway. He was an organizer of the North American Life and Casualty Insurance Company and a member of its board of directors for many years. He was a member of the American Medical Association, Goodhue County Medical Society, and a 50 Club and associate member of the Minnesota State Medical Association.

He is survived by his wife, a daughter, and a son, Dr. A. Russell Aanes of Tucson.

JOHN EDWARD TWOMEY, M.D.

Dr. John E. Twomey, 45, chief of staff at St. Mary's Hospital in Minneapolis since 1962, died November 30. He was born in Brockway, Minnesota, and graduated from the University of Minnesota Medical School.

Dr. Twomey was a clinical instructor in surgery at the University of Minnesota, served on the Glen Lake Sanatorium Commission, the General Hospital and Health Advisory Board, and the board of the Minneapolis War Memorial Blood Bank. Under his chairmanship, a cancer clinical research program and tumor registry was initiated at St. Mary's in 1959. He was a member of the American Medical Association, Minnesota State Medical Association and Hennepin County Medical Society.

He is survived by his wife, a daughter and three sons.

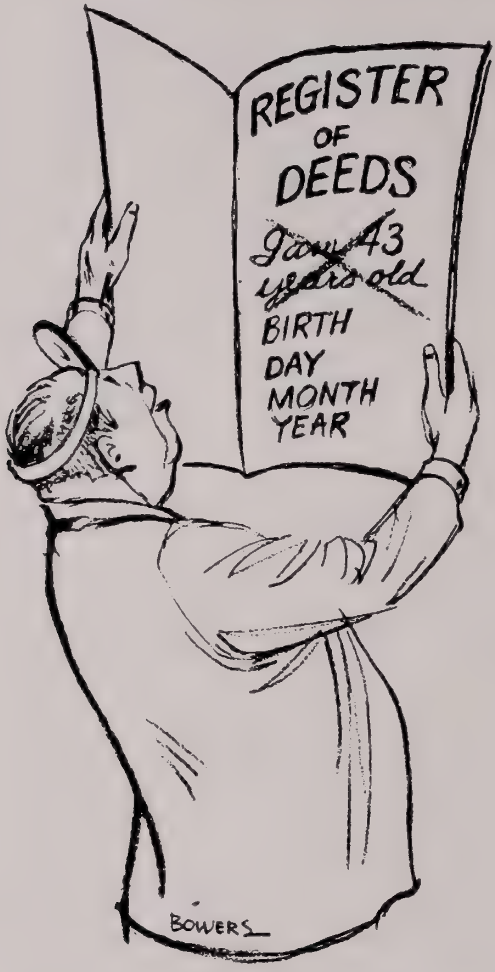
FLOYD A. THOMPSON, M.D.

Dr. Floyd A. Thompson, 62, St. Paul pediatrician, died November 24, after a lengthy illness. Born in Minneapolis, he had resided in St. Paul fifty-five years, and practiced medicine there for thirty-four years.

He received his medical degree from the University of Minnesota, and was a former chief-of-staff at St. Lukes Hospital in St. Paul. He was a member of the Academy of General Practice, American Medical Association, Minnesota State Medical Association and Ramsey County Medical Society.

He is survived by his wife.

Better Service, Doctor?



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Meetings and Announcements

Gratuitous violence in argument betrays a conscious weakness of the cause, and is usually a signal of despair. — Junius

JANUARY

Hennepin County Medical Society, January 3, 6:00 p.m., Pick-Nicollet Hotel, Minneapolis.

Hennepin County Psychiatric Society, January 3, Held in connection with Hennepin County Medical Society.

Zumbro Valley Medical Society, January 5, 8:00 p.m., Mann Hall, Rochester, new officers take positions.

Minnesota Academy of General Practice & Hennepin County Medical Society, January 10, Lederle Symposium, all day, Radisson Hotel, Minneapolis.

Minnesota Academy of Medicine, January 12, 6:30 p.m., Town & Country Club, St. Paul.

St. Louis County Medical Society, January 13, Executive Committee, 6:00 p.m., St. Mary's Hospital, Duluth. Annual business meeting, 8:00 p.m.

Twin City Urological Society, January 21, 6:00 p.m., Town & Country Club, St. Paul.

Ramsey County Medical Society, January 31, 8:00 p.m., 1500 Lowry Medical Arts Building, St. Paul.

American College of Surgeons Sectional Meeting, Bal Harbour, Florida, January 13-15, Americana Hotel. Contact: American College of Surgeons, 55 East Erie Street, Chicago.

30th Annual Session of the International Medical Assembly of Southwest Texas, January 24-26, Granada Hotel, San Antonio Texas. Contact: Bernard Fein, 202 W. French Place, San Antonio.

American College of Surgeons Sectional Meeting in Houston, Texas, January 31-February 2 at Shamrock-Hilton Hotel. Contact: College at 55 East Erie Street, Chicago.

American College of Cardiology postgraduate course, January 19-21 "John J. Hartigan Memorial Seminar," Peter Bent Brigham Hospital, Boston and January 20-22 "Unresolved Problems in Cardiology," Mount Sinai Hospital, Miami Beach. Florida. Contact: College in Washington, D. C.

Minnesota Academy of Ophthalmology and Oto-Laryngology meeting January 14, Minneapolis Athletic Club.

FEBRUARY

Minnesota Academy of Medicine meeting, February 9, Town & Country Club, St. Paul, 6:30 p.m.

St. Louis County Medical Society Executive Committee Meeting, February 10, 6:00 p.m., St. Luke's Hospital, Duluth. Business Meeting at 8:00 p.m.

Twin City Urological Society Meeting, February 18, Town and Country Club, 6:00 p.m., St. Paul.

Ramsey County Medical Society Meeting, February 28, 1500 Lowry Medical Arts Building, St. Paul, 8:00, p.m.

Sioux Valley Medical Association Meeting, February 24-25, Sheraton-Warrior Motor Inn, Sioux City, Iowa. Contact: D. M. Youngblade, M.D., 2417 Pierce St., Sioux City.

ANNOUNCEMENTS

Conference on Pediatric and Adolescent Gynecology will be held March 24, through March 26, 1966, at the Waldorf-Astoria in New York City, under the auspices of the New York Academy of Sciences. Contact: Warren Lang, M.D.; Jefferson Medical College of Philadelphia, 1025 Walnut Street, Philadelphia.

* * *

Dr. Birger Strandell, a member of the faculty of the Caroline Institute, Stockholm, and editor of ACTA MEDICA SCANDINAVICA, will lecture on "Linnaeus" at Rochester, May 10, 1966. The lecture, sponsored by the Mayo Foundation chapter of Sigma XI, will be held a day before the opening of the annual meeting of the American Association for the History of Medicine. Contact: Thomas E. Keys, 200 First Street Southwest, Rochester, Minnesota.

* * *

The twenty-ninth annual meeting of The New Orleans Graduate Medical Assembly will be held March 7, 8, 9 and 10, 1966, headquarters at The Roosevelt Hotel.

Nineteen outstanding guest speakers will participate and their presentations will be of interest to both specialists and general practitioners. This program is acceptable for twenty-nine (29) accredited hours by the American Academy of General Practice, Write Secretary, New Orleans Graduate Medical Assembly, 1430 Tulane Avenue, Room 1528, New Orleans, Louisiana 70112.

* * *

The William Osler Medal of the American Association for the history of medicine is awarded for the best unpublished essay on a medico-historical subject written by a medical student. Contact: William Beatty, 303 East Chicago Avenue, Chicago.

Classified

Classified advertising rates are twenty (20) cents a word; minimum monthly charge $5.00; key number, fifty (50) cents additional.

Replies to advertisements with key numbers should be mailed in care of MINNESOTA MEDICINE, *496 Lowry Medical Arts Bldg., St. Paul, Minn. 55102*

PHYSICIAN — TB and Geriatric State Hospital; accredited; $12,828.00-$15,600.00 based on qualifications and experience; desirable suburban location; residence available; liberal sick leave and vacation benefits; excellent retirement system. Contact: Medical Director, Glen Lake State Sanatorium, Minnetonka, Minnesota.

TWO G.P.'s NEEDED — Northern Minnesota county seat. New hospital, office space available, two other physicians in town, anesthetist on hospital staff, good schools, all churches, excellent hunting and fishing, housing available. Full details upon request. Contact: Administrator, Roseau Area Hospital, Roseau, Minnesota.

BADLY NEEDED — G.P., Internist or Surgeon to associate with two-man G.P. partnership. Unopposed territory. New hospital, nursing home, children's home! Superb hunting, fishing, golf, pool, winter arena. Progressive town! Delmore Clinic, Roseau, Minnesota 56751.

PART TIME INTERNIST OR GENERAL PRACTITIONER. Good compensation — Midway Area. Alfred F. Anderegg, M.D.; 2500 Como Avenue, St. Paul, Minnesota.

WANTED: Board Certified or eligible internist to associate with group in large, active practice in Minneapolis. Group consists of Surgeon, Obstetrician, Pediatrician and Internist maintaining downtown and suburban offices. Partnership in mind. Contact: Jesse J. Barron, M.D., 1127 Medical Arts Building, Minneapolis, Minnesota 55402, FEderal 2-8259.

OLD, WELL ESTABLISHED multi-specialty group of 23 doctors in Midwestern city has opening for board certified or eligible specialists as follows: orthopedic surgeon, internist, pediatrician, otolaryngologist. All departments established and growing. Well-equipped clinic and excellent hospital facilities in community. Attractive financial plan leading to full partnership. Include curriculum vitae. Full expenses paid for applicants invited for interview. Write: MINNESOTA MEDICINE — 337; 496 Lowry Medical Arts Building, St. Paul 55102.

BUSY, GROWING aggressive 3-man partnership in Northwest Wisconsin serving a trade area of 15,000 needs a well-trained recent graduate with fulfilled military obligations to associate immediately on excellent salary, with partnership in 1 year if mutually agreeable. Modern 15 room air conditioned brick clinic building is being doubled in size this year. 32 bed hospital and new 42 bed nursing home one minute from clinic. New 1500 student consolidated school. Excellent hunting, fishing and outdoor sport facilities in immediate area. Contact: MINNESOTA MEDICINE — 317; 496 Lowry Medical Arts Building, St. Paul 55102.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with early partnership. Write: MINNESOTA MEDICINE — 289; 496 Lowry Medical Arts Building; St. Paul, 55102.

WANTED: Generalist to associate with two man partnership in Northern Minnesota. Community has a thirty-seven bed hospital, X ray and laboratory technicians and nurse anesthetist. Good hunting and fishing. Adequate salary and time off. Contact: A. G. Janecky, M.D., Baudette Clinic, Baudette, Minnesota.

OFFICE SPACE now available in busy Bloomington. 713 square feet of new space in building with busy group of G.P.'s, dentist and suburban OB-GYN office. Ideal for ophthalmology, ENT or pediatrics. 8040 Penn Avenue South. 888-9211.

WANTED: one or two general practitioners. Excellent clinic and hospital facilities. Rural practice established 18 years. Salary open, partnership if compatible. Lloyd H. Klefstad, M.D., Greenbush, Minnesota.

SACRED HEART, MINNESOTA, doctorless since 1961, wants general practitioner. Population 700, accredited hospital 10 miles away. Write: Rev. Robert Bardy, Phone 765-2547, Sacred Heart, Minnesota.

A THREE MAN group needs a fourth general practitioner in a fast-growing West St. Paul area. Begin with salary and join partnership with full participating advantages. Write: MINNESOTA MEDICINE — 326, 496 Lowry Medical Arts Building, St. Paul 55102.

GENERAL PRACTITIONER WANTED: to associate with physician-surgeon in Owatonna, a Southern Minnesota community, 25,000 population. Clinic building three years old; with five large treatment rooms, lab.; x ray; central supply; two doctors' offices; pharmacy; and business offices. Located next door to 85-bed city hospital. Good opportunity for partnership. Contact: O. W. Roberts, M.D.; 920 South Cedar Street; Owatonna, Minnesota. Phone 451-4630.

LOCUM TENENS wanted for general practice in St. Paul from mid-February through March, 1966. Write: MINNESOTA MEDICINE — 328; 496 Lowry Medical Arts Building, St. Paul 55102.

MEDICAL ART. Drawings, charts and lettering for publication, slide lectures, movies, exhibits and television. Also three dimensional models. Al Hage — 339-1012, Minneapolis.

GENERAL PRACTITIONER AVAILABLE. Completing military June, 1966. Five years experience; married, desires group practice Rochester, Minneapolis, St. Paul or surrounding area, minimum OB and surgery. Write MINNESOTA MEDICINE — 331, 496 Lowry Medical Arts Building, St. Paul, Minnesota.

WANTED: young general practitioner to join six-man group consisting of 4 GPs, a general surgeon, and radiologist. College town of 5,500, 30 miles from Twin Cities. Also need LOCUM TENENS in general practice. Contact: Ed Jenkins, Mgr., River Falls Medical Clinic, River Falls, Wisc. Phone 425-5322.

WANTED locum tenens for month of February 1966. Can live in my home. If married, bring wife and children. Modern hospital and clinic, consultation available. Contact as soon as possible by mail or telephone: Wm. C. Heiam, M.D., Cook, Minnesota. Telephone: 666-3354 or 666-2261.

PHYSICIAN (General Medicine or Surgery) at 245-bed VA General Hospital in scenic Black Hills. Area offers excellent hunting, fishing, recreation. Requirements: Graduate approved school, citizenship, license any state, salary based on qualifications, housing available. Nondiscrimination in employment. Contact Chief of Staff, VA Center, Hot Springs, South Dakota 57747.

WANTED SOMEONE in East Side St. Paul general practice who would desire temporary locum tenens, one, two or three months. Write: MINNESOTA MEDICINE — 335, 496 Lowry Medical Arts Building, St. Paul 55102.

WANTED: Generalist desiring fast start in too busy St. Paul practice. No covenants or contingent clauses. You move to available nearby independent office facilities as soon as you establish an adequate following of your own, or you stay as a partner if you desire. Incidentally lousy working conditions: new building, built-in Hi-fi, every third week off. If you desire to establish yourself permanently in present location. You name your own terms. Write MINNESOTA MEDICINE — 336, 496 Lowry Medical Arts Building, St. Paul 55102.

WANTED: Immediate opening for young GP in an established medical corporation. Three man G.P. group located in rapid-growing North Suburban Metropolitan Area. 15 minutes from loop and large educational center. New clinic. New 150-bed hospital. Salary open, fringe benefits. Fridley Medical Center, P.A., 203 Mississippi Street, Minneapolis, Minnesota 560-2950.

FOR RENT: Successful medical building. Will help doctor or group of doctors get started in proven location in Northwest Suburban Minneapolis, 36th and Noble near two hospitals. Call or write Noble Drug, 4705 36th Avenue North, Minneapolis 22. Ju 8-9449.

WANTED — Internist, board certified or qualified, to associate with two board certified internists. Ten man multi-specialty group. (Lenont Peterson Clinic, Virginia, Minnesota) — Heart of the expanding taconite industry.

FOUR STAFF ADDITIONS to Southern California Group of 24 physicians. Internist with chest subspecialty, ophthalmologist, otolaryngologist, general practitioner. Partnership possibility after first year. Administrator, Gallatin Medical Group, 10720 S. Paramount Blvd., Downey, Calif.

WANTED: Young internist and pediatrician, board certified or eligible, to join 6-man group consisting of 4 GP's, a general surgeon, and a radiologist. College town of 5,500 only 30 miles from Twin Cities. Salary open with early partnership opportunity. Write or call collect: Ed Jenkins, Mgr., River Falls Medical Clinic, River Falls, Wisc., phone 425-5322.

EXCELLENT and immediate opening for one or two physicians. 17-bed fully-equipped municipal hospital with lab and x-ray facilities. Also private 40 bed nursing home. Complete clinic, including equipment, available for rent. Doctor owner retiring because of ill health. No investment needed. Prosperous agricultural community. Opportunity for rewarding lifetime practice. Phone 669-4421 collect, Clarkfield, Minnesota Hospital.

PSYCHIATRIC RESIDENCIES, positions available July 1966. Fully approved, balanced didactic and clinical experiences. Five-year career program: $8,895, $10,294, $12,048, $15,368, $16,203; NIMH general practitioner stipends $12,000 annually for three years in Michigan's water winter wonderland. Paul E. Kauffman, Ph.D., Director of Resident Training, Traverse City State Hospital, Traverse City, Michigan. An equal opportunity employer.

WANTED: General practitioner able to do surgery. Present physician wanting to "semi-retire." Good community, prosperous farming. Good schools and churches. New hospital and clinic buildings. Contact: Warren Clinic, P.O. Box 107, Warren, Minnesota 56762.

WANTED: Young G.P. for rural practice partnership. No initial investment. Previous partner and well-equipped for dual practice. Good hospital — 12 miles and large medical center 30 miles on four lane highway. Small town in stable farming community, resort area, hunting and fishing, good school system. Contact: A. S. Midthune, M.D., Lake Park, Minnesota.

RELAXED, GRACIOUS COUNTRY LIVING viewing St. Croix River. Spacious, 3-bedroom, modern home on two acres — amidst stately shade trees. Recreation room. 17 miles to St. Paul. Write: Harlan Fisher, Route 5, Stillwater, Minnesota. Telephone 436-8844.

CHIEF OF PSYCHIATRIC SUPERVISORY STAFF needed to help with clinical supervision and teaching in expanding (18 Resident Physicians) fully-approved residence training program. Ideal living in active community in the heart of Michigan's Water-Winter Wonderland. Newly established position requires board certification in psychiatry and additional experience in clinical supervision. Salary range depending upon qualifications, $17,383 to $21,339 with liberal Michigan civil service benefits. Contact Arthur F. Dundon, M.D., Clinical Director, Traverse City State Hospital, Traverse City, Michigan. An equal opportunity employer.

GENERALIST NEEDED. Death of associate in three-man group in general practice in White Bear Lake, Minnesota, requires immediate replacement. Salary with advancement to partnership negotiable. Excellent opportunity for young man in an established practice of young men (under 38 years old). New building in suburban area of St. Paul. Locum tenens also considered. Call or write: A. J. Rushay, M.D. or T. G. Briggs, M.D., 777-1341.

PHYSICAL MEDICINE AND REHABILITATION RESIDENCY — Approved 3-year program integrated with the University of Minnesota. Active service, 1,000 bed general hospital. Career residency salary $8,961-$12,510, non-career resident $4,325-$6,035 plus fringe benefits. Non-discrimination in employment. Contact PM&R Service, Veterans Administration Hospital, Minneapolis.

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Contraindications: Benactyzine hydrochloride is contraindicated in glaucoma. Previous allergic or idiosyncratic reactions to meprobamate contraindicate subsequent use.

Precautions: *Meprobamate*—Careful supervision of dose and amounts prescribed is advised. Consider possibility of dependence, particularly in patients with history of drug or alcohol addiction; withdraw gradually after use for weeks or months at excessive dosage. Abrupt withdrawal may precipitate recurrence of preexisting symptoms, or withdrawal reactions including, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, the dose should be reduced and operation of motor vehicles or machinery or other activity requiring alertness should be avoided if these symptoms are present. Effects of excessive alcohol may possibly be increased by meprobamate. Grand mal seizures may be precipitated in persons suffering from both grand and petit mal. Prescribe cautiously and in small quantities to patients with suicidal tendencies.

Side effects: Side effects associated with recommended doses of 'Deprol' have been infrequent and usually easily controlled. These have included drowsiness and occasional dizziness, headache, infrequent skin rash, dryness of mouth, gastrointestinal symptoms, paresthesias, rare instances of syncope, and one case each of severe nervousness, loss of power of concentration, and withdrawal reaction (status epilepticus) after sudden discontinuation of excessive dosage.

Benactyzine hydrochloride—Benactyzine hydrochloride, particularly in high dosage, may produce dizziness, thought-blocking, a sense of depersonalization, aggravation of anxiety or disturbance of sleep patterns, and a subjective feeling of muscle relaxation, as well as anticholinergic effects such as blurred vision, dryness of mouth, or failure of visual accommodation. Other reported side effects have included gastric distress, allergic response, ataxia, and euphoria.

Meprobamate—Drowsiness may occur and, rarely, ataxia, usually controlled by decreasing the dose. Allergic or idiosyncratic reactions are rare, generally developing after one to four doses. Mild reactions are characterized by an urticarial or erythematous, maculopapular rash. Acute nonthrombocytopenic purpura with peripheral edema and fever, transient leukopenia, and a single case of fatal bullous dermatitis after administration of meprobamate and prednisolone have been reported. More severe and very rare cases of hypersensitivity may produce fever, chills, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, anaphylaxis, stomatitis and proctitis. Treatment should be symptomatic in such cases, and the drug should not be reinstituted. Isolated cases of agranulocytosis, thrombocytopenic purpura, and a single fatal instance of aplastic anemia have been reported, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity has been reported, usually after excessive meprobamate dosage. Suicidal attempts may produce lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

Dosage: Usual starting dose, one tablet three or four times daily. May be increased gradually to six tablets daily and gradually reduced to maintenance levels upon establishment of relief. Doses above six tablets daily are not recommended even though higher doses have been used by some clinicians to control depression and in chronic psychotic patients.

Supplied: Light-pink, scored tablets, each containing meprobamate 400 mg. and benactyzine hydrochloride 1 mg.
Before prescribing, consult package circular.

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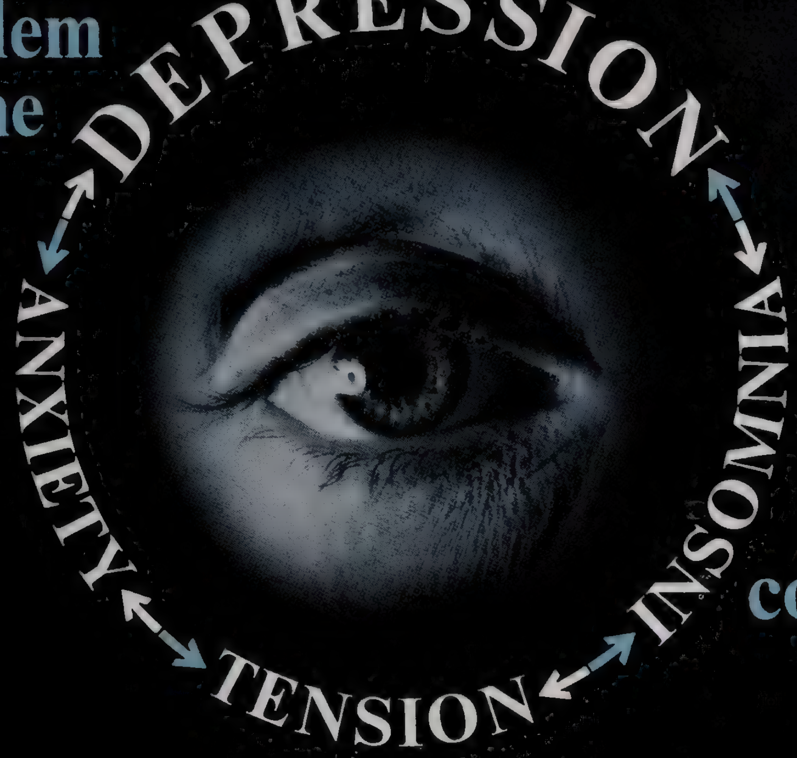
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by helping
to lift depression…
calm associated anxiety,
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March 7, 8, 9, 10, 1966

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Robert J. Rowe, M.D., Dallas, Tex.—*Colon and Rectal Surgery*
Walter C. Lobitz, Jr., M.D., Portland, Ore.—*Dermatology*
Bernard J. Haverback, M.D., Los Angeles, Calif.—*Gastroenterology*
Joseph J. Rupp, M.D., Philadelphia, Pa.—*General Practice*
Roy T. Parker, M.D., Durham, N. C.—*Gynecology*
Stefan S. Fajans, M.D., Ann Arbor, Mich.—*Internal Medicine*
John S. LaDue, M.D., New York, N. Y.—*Internal Medicine*
Joseph M. Foley, M.D., Cleveland, Ohio—*Neurology*
Duncan E. Reid, M.D., Boston, Mass.—*Obstetrics*
H. Saul Sugar, M.D., Detroit, Mich.—*Ophthalmology*
S. Benjamin Fowler, M.D., Nashville, Tenn.—*Orthopedic Surgery*
Walter P. Work, M.D., Ann Arbor, Mich.—*Otorhinolaryngology*
William O. Russell, M.D., Houston, Tex.—*Pathology*
William A. Silverman, M.D., New York, N. Y.—*Pediatrics*
C. Allen Good, M.D., Rochester, Minn.—*Radiology*
Louis M. Rousselot, M.D., New York, N. Y.—*Surgery*
Jerome A. Urban, M.D., New York, N. Y.—*Surgery*
Donald R. Smith, M.D., San Francisco, Calif.—*Urology*

Additional Speaker to be Announced

Lectures, symposia, clinicopathologic conferences, round-table luncheons, medical motion pictures, technical exhibits and entertainment for visiting wives. (All-inclusive registration fee—$25.00).

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For information concerning the Assembly meeting and tour write Secretary, The New Orleans Graduate Medical Assembly, Room 1528, 1430 Tulane Avenue, New Orleans, Louisiana 70112.

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Physician's Diary

Life is to be fortified by many friendships. — To love and to be loved is the greatest happiness of existence. — Sydney Smith

NEW LOCATIONS: **Dr. L. Ashley Whitesell, Jr.** of Shakopee, has joined Drs. Catlin and Sandeen at the Buffalo Clinic . . . **Dr. Bernard Hanson** of Moorhead will practice in Bigfork . . . **Dr. Brandon Adams** has joined **Dr. D. H. Dewey** as an associate in Owatonna . . . **Dr. Dallas Glick** and **Dr. Alvin Wiens** have become associated in Mountain Lake.

* * *

New officers of the Minneapolis Ophthalmological Society are: **Joseph L. Garten, M.D.,** president and **Irving Shapiro, M.D.,** secretary.

* * *

Dr. Herb L. Huffington of Waterville has assumed the presidency of the Minnesota Academy of General Practice.

* * *

Dr. Karl W. Anderson of Excelsior, a member and treasurer of the Minnesota State Medical Association, was given the Harold S. Diehl award of the University of Minnesota Medical Alumni Association recently.

* * *

Dr. Hugh R. Butt, head of a section of medicine in the Mayo Clinic, was a visiting professor of medicine at the National Institute of Arthritis and Metabolic Diseases, Public Health Service, Bethesda, Maryland, November 15th, where he participated in medical rounds and seminars.

* * *

Roger P. Hallin, M.D. of Minneapolis has been named a director of the rehabilitation services of the Kenny Rehabilitation Institute.

* * *

Dr. Donald E. Stewart, Crookston, surgeon, has been elected president and board chairman of the Minnesota Division of the American Cancer Society.

* * *

Dr. Traz Akhavan, a native of Iran, has arrived in Alexandria to establish the Douglas County Diagnostic Laboratory.

Dr. Louis A. Brunsting, emeritus head of the Section of Dermatology of the Mayo Clinic, was reelected president of the American Board of Dermatology at its annual meeting.

* * *

Dr. Glen Gullickson, Jr. of Minneapolis was recently presented with "Golden Keys" by the American Congress of Physical Medicine and Rehabilitation. This is the highest honor the group confers.

* * *

The Minnesota Heart Association awarded grants to the following physicians: **Doctors Victor Lorber, Lewis Wannamaker** of St. Paul, **Dr. Earl H. Wood** of Rochester, and **Doctors Elia Ayoub, Ivan Frantz, Robert Good, Alfred Michael, Jr., Raymond D. A. Peterson and Joseph W. St. Geme, Jr.** of the University of Minnesota.

* * *

Dr. William L. Benedict, emeritus head of the Section of Ophthalmology; **Dr. Howard P. Rome,** senior consultant in psychiatry; and **Dr. James C. Cain** consultant in medicine, all of the Mayo Clinic, were named delegates to the White House Conference on Health held in Washington, D. C. in November.

* * *

The St. Paul Society of Psychiatry & Neurology was recently formed for the purpose of cultivating and improving the science and art of psychiatry and neurology in the greater St. Paul metropolitan area. There are presently twenty-five active members. Officers of the newly formed society are: **Dr. E. M. Hammes, Jr.,** president; **Dr. Robert Gumnit,** vice-president and **Dr. Glenn M. Lewis,** secretary.

* * *

The Interstate Clinic in Red Wing unofficially celebrated its 25th anniversary in September. The clinic opened with four doctors and three employees, and in the intervening years, has increased these figures to nine doctors and 30 employees.

* * *

Doctors Lynwood H. Smith, Ralph S. Zitnik, John W. Beabout, Edward J. O'Connell, Jorge E. Maldonado and John N. Simons have been appointed to the staff of the Mayo Clinic in Rochester.

Minnesota Medicine at a Glance

Aneurysmal Abscess — Huebl and Read Page 11

Although infection is an unusual cause of aneurysm, the intra-arterial administration of either angiographic media or, in addicts, concentrated paregoric mixtures have caused it in four cases. They involved the common carotid and femoral vessels and presented as pulsating abscesses.

Treatment was ligation of the involved vessel, incision, and wide drainage. One patient died subsequently of pneumonia and septicemia. The role played by extravasation, intramural injection, contamination, and chemical necrosis has been discussed, as well as the question of immediate or delayed reconstructive procedures.

Diagnostic Test for Coronary Disease — Cohen et al. Page 17

A new test for the detection of coronary artery disease is described. The procedure involves a coincidence counting method and the use of a positron emitter, rubidium^{84}. The coronary blood is measured by the logarithmic extrapolation of the myocardial clearances. Catheterization of the coronary sinus is not necessary; only a venous and an arterial puncture are performed. The data are objectively calculated by a digital computer.

Nitroglycerin increases the coronary blood flow in patients without coronary artery disease while failing to do so in individuals with coronary artery disease; this finding has become the basis for a diagnostic test in the recognition of coronary artery disease.

Pyoderma Gangrenosum — Altman and Mopper Page 22

Pyoderma gangrenosum is a rare, chronic, ulcerative skin disease beginning as a cutaneous abscess which rapidly breaks down to form large peripherally spreading ulcerations with a distinctive purple-red edematous and undermined border. It is frequently associated with chronic debilitating diseases, particularly ulcerative colitis.

The treatment is difficult: but the use of sulfone drugs, as illustrated in two cases, is effective in the long-term care of this condition. Sulfone drugs do not produce allergic cross reactions with sulfonimides and appear to be well tolerated in patients who are sensitive to sulfonimides.

Intracranial Hemorrhage — Chason et al. Page 27

Intracerebral hemorrhage accounts for approximately 200,000 deaths and it has been estimated that 2,000,000 people survive this cerebral vascular disease each year. In this study all individuals who die from this condition have suffered hypertension.

With the advent of relatively new procedures in the surgical correction of this disabling disease, the autopsy studies in this manuscript merely point out the urgency of pursuing more active treatment for patients who suffer from "stroke." It need not be a fatal or disabling disease.

The Carcinoid Syndrome — Circulatory and Cardiac Manifestations
— Zobl et al. Page 39

The carcinoid syndrome, ordinarily considered to be an invasive-type tumor, arising in the ileum with metastatic extension to the liver and heart, manifests its principal symptom by the production of an excessive amount of serotonin. In this instance, the symptoms consisted principally of facial flushing, sweating, weakness, abdominal cramps, and diarrhea.

In addition to the abnormally high serotonin levels, cardiac-catheterization studies revealed increased pulmonary artery pressure and abnormally high serum-histamine and catecholamine levels. It was suggested that these studies indicate that there are other basic, active substances in the circulating blood of patients suffering from the carcinoid syndrome.

Patch-Grafting — Thal et al. Page 45

There are occasions when a defect in the duodenum cannot be satisfactorily bridged and to close it without adequate patency has proven to be uniformly unsatisfactory.

Thal et al. have followed the procedure of applying an adjacent loop of serosa to fill in the defect which in effect then results in a shallow ulcer. This in turn rapidly heals as the ingrowing mucosa closes over the ulcer. The technique of this procedure is well illustrated in the manuscript.

Pulmonary Surgery for Emphysema — Hymes and Berkas Page 50

Patients with severe emphysema are excessive smokers who have pulmonary distress. In some instances when the cysts are large they are found to be tuberculous.

Without performing a pulmonary resection it is possible to give these patients considerable relief by removal of the cysts and obliteration of the pleural cavity. Poor pulmonary function is not a contraindication for surgery. Because giant air spaces are anatomically on the surface of the lung one need not remove the lobe or an extensive lung segment.

Cerebral Vasospasm — Thomas et al. Page 55

Though the concept of vasospasm as an etiologic factor in the production of cerebral disfunction, with intermittent attacks of paralysis, weakness, or dysphasia, has been recently disclaimed, the studies of Thomas et al. reveal that the topical application of certain drugs does produce vasoconstriction or vasodilatation. When given intravenously only papaverine produces vasodilatation.

Zinc Deficiency Syndrome — Prasad Page 59

A zinc-deficiency syndrome has been described for the first time and presents, in its clinical manifestations, a severe iron-deficiency anemia, hepatosplenomegaly, hypogonadism, dwarfism, and geophagia.

Metabolic studies indicate that the zinc content of the plasma, red blood cells, and hair was reduced, and that the excretion of zinc in the urine and stool was diminished.

Continued

When adequate diet and supplemental zinc were administered, the subjects under observation showed marked improvement: a marked increase in stature and a growth of external genitalia. Associated with this was an increase in the follicular stimulating hormone in the urine after the institution of treatment. It is obvious that in patients with iron-deficiency anemia one must also look for associated zinc deficiency.

Neonatal Gastric Rupture — Silbergleit and Berkas Page 67

Rupture of the stomach is the most common visceral perforation in the infant, occurring usually in the first few days of life. It is more common in premature infants, usually comes on suddenly, and is evidenced by a distended abdomen filled with air.

It has been thought that this condition is caused by peptic ulcer, distal obstruction, or trauma. Experimental studies on the dog indicate that distention of the stomach above 196 mm. of mercury will cause a stomach to rupture. It is speculated that the increased intra-abdominal pressure on the unborn child during the delivery could lead eventually to complete rupture of the gastric wall.

As soon as the diagnosis can be made surgery must be performed to close the defect.

Jaw Fractures — Monaco et al. Page 113

When an individual has a full complement of teeth and a jaw fracture, the problems are not as difficult as when an individual tooth is broken or when the jaw is edentulous.

The problem of treatment involves the restoration of the proper vertical-occlusal dimensions of the face. When this has been accomplished the results are usually very satisfactory. The technique of wiring a comminuted fracture is graphically illustrated.

Blind-End Ureter — Gonick Page 121

A man of 56 years had dull recurrent flank pain for 25 years, and his first investigative studies revealed pyuria with duplication of the right ureter and nonfunction of the left. These symptoms continued until he finally submitted himself for full evaluation and therapy. The persistent pyuria was finally identified as being due to a blind ureter on the left side, associated with a double ureter in the same kidney. After removal of the involved kidney he was relieved of his symptoms. It was concluded that this represented a combined neuromuscular defect which allowed urine to be refluxed into the blind ureter under the low pressure of a partly filled bladder, thus setting up the mechanism for chronic infection.

Complications of Anticoagulant Therapy — C P C Page 145

This represents the experience in one patient, in whom it appears that excessive anticoagulant therapy produced extensive bleeding in the epidural area of the cord, resulting in transverse myelitis.

Other complications of anticoagulant therapy are reviewed, and the lesson to be learned is that such therapy cannot be prescribed lightly without frequent clinical observations of the patient.

One of the most tragic cases reported in literature is the fatal hemorrhage in the nursing infant of a mother who was on anticoagulant therapy.

Traumatic Aortic Aneurysm — Berkas et al. Page 153

Traumatic aortic aneurysm may result from a major chest trauma, and if manifest as an acutely developed aneurysm the patient may present severe symptoms with evidence of blood loss. Dysphagia, dyspnoea, cough, and hoarseness are symptoms of a aneurysmal mass exerting pressure on the esophagus, bronchus, or recurrent laryngeal nerve.

Diagnosis is made on the basis of an extending mediastinal mass and can be confirmed by performing a retrograde aortogram. Operative repair can result in the salvage of a person who has a single correctable defect of this nature.

Basic Enzymology in Blood Clotting — Seegers Page 171

This is a masterful description of the basic enzymology in bloodclotting and can be thoroughly understood only by devoting conscientious moments to studying it.

The inability of many physicians to prepare a medical manuscript is a chronic, slowly developing disorder, which, unless treated relentlessly and vigorously, can progress to complete agraphia. Commonly called writer's syndrome, the disease is characterized by weakness, redundancy, indistinctness, triteness, endlessness, and rejection slips.

M. Therese Southgate, M.D.
Journal of the American Medical Association

Worry, according to a contemporary biochemist, "can be chemically defined as the psychic reaction of somatic saturation with paralytic acid and monosodic phosphate." — American Hebrew

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Where all think alike, no one thinks very much. — Walter Lippmann

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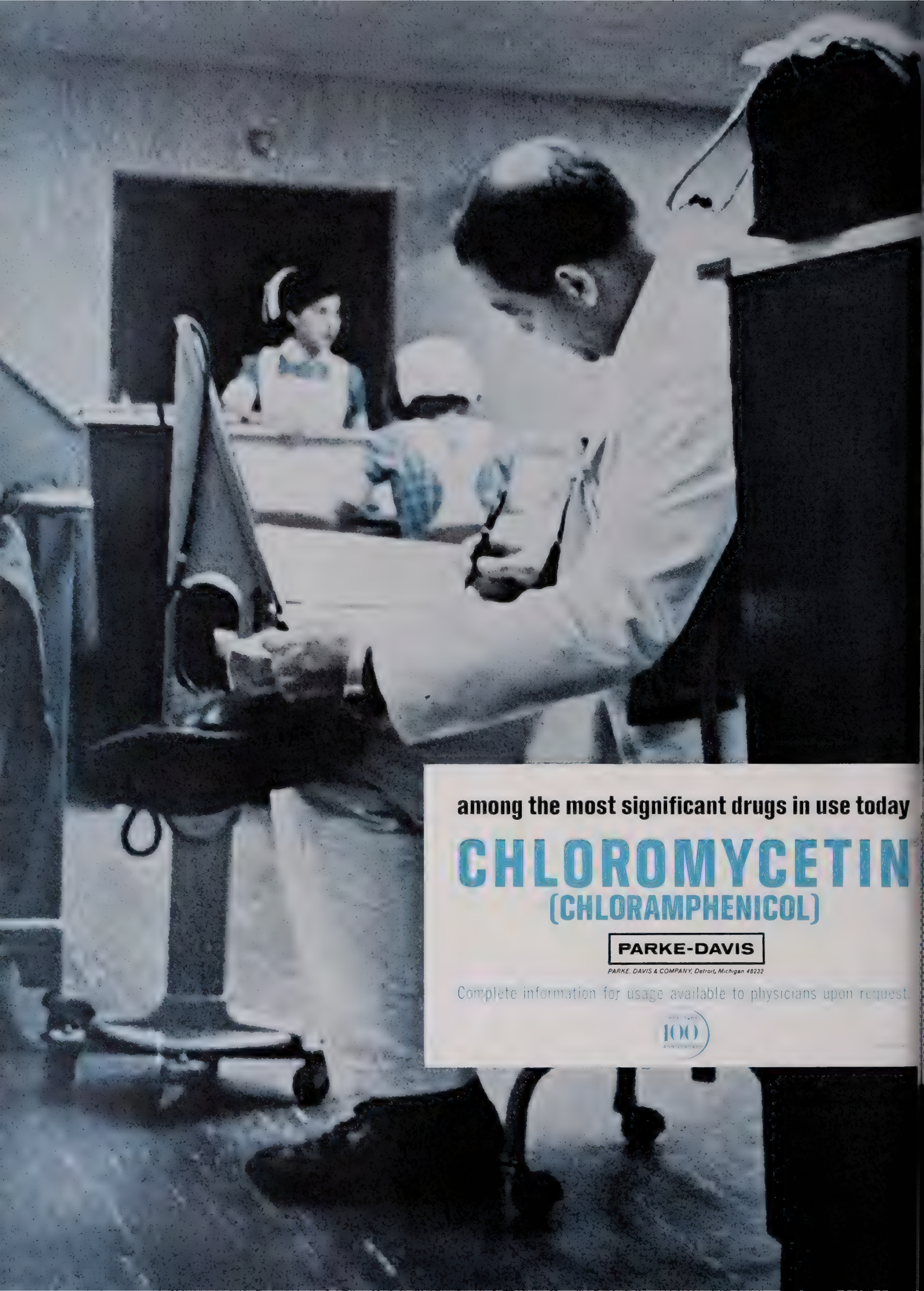

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Minneapolis, Minnesota

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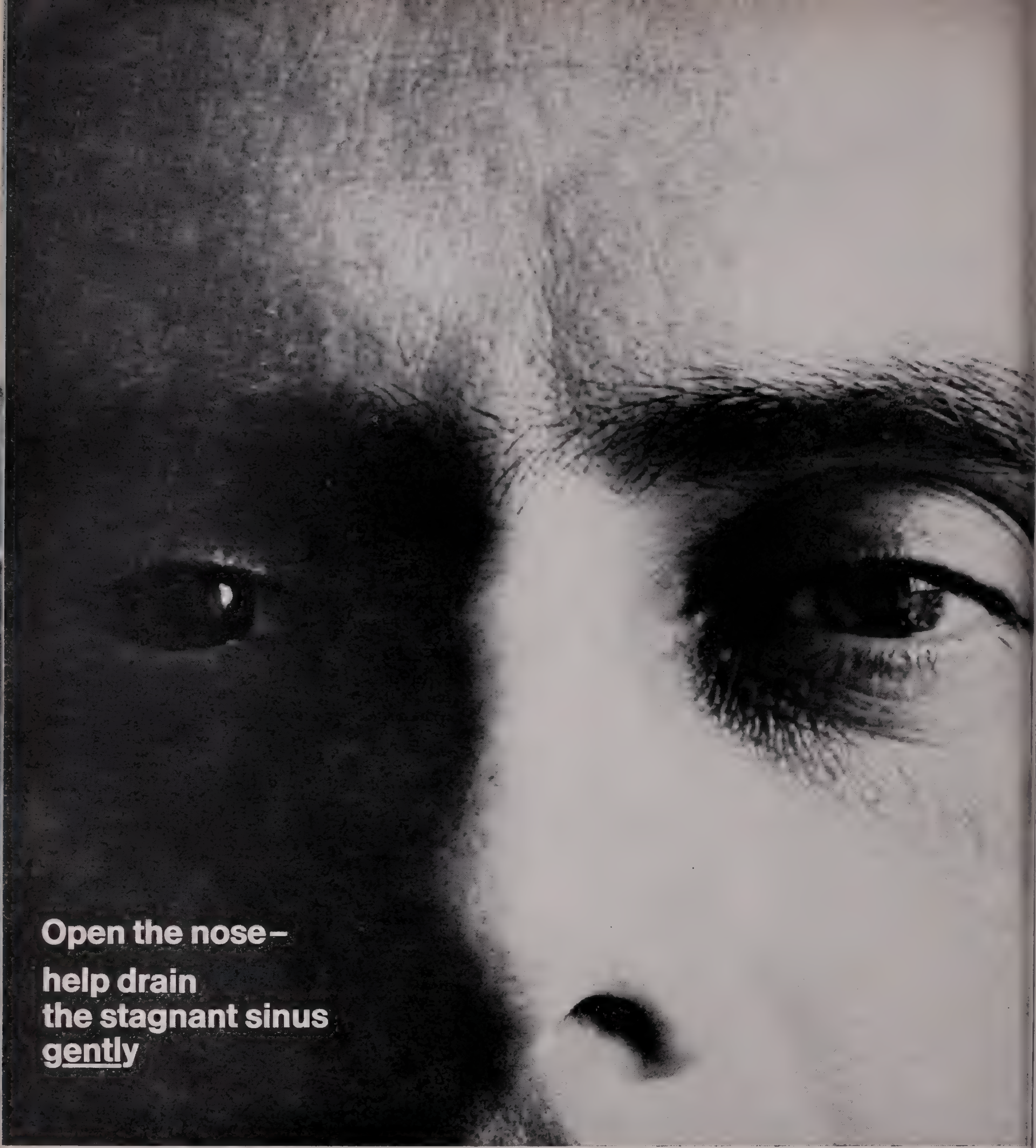

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*Proctor, D. F.: The Nose, Paranasal Sinuses, and Ears in Childhood, Springfield, Ill., Charles C Thomas, 1963, p. 34.

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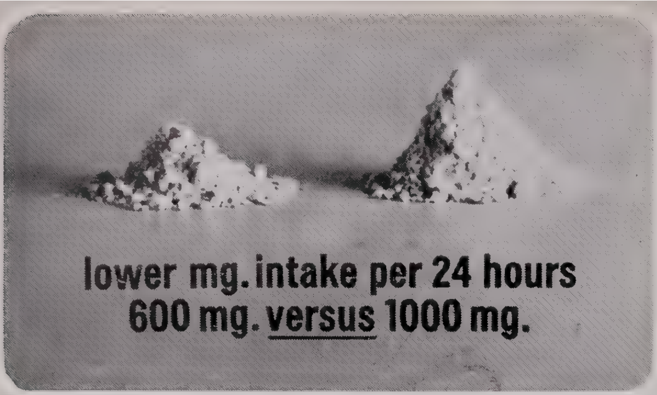

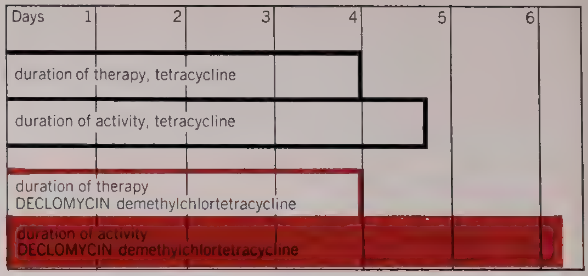

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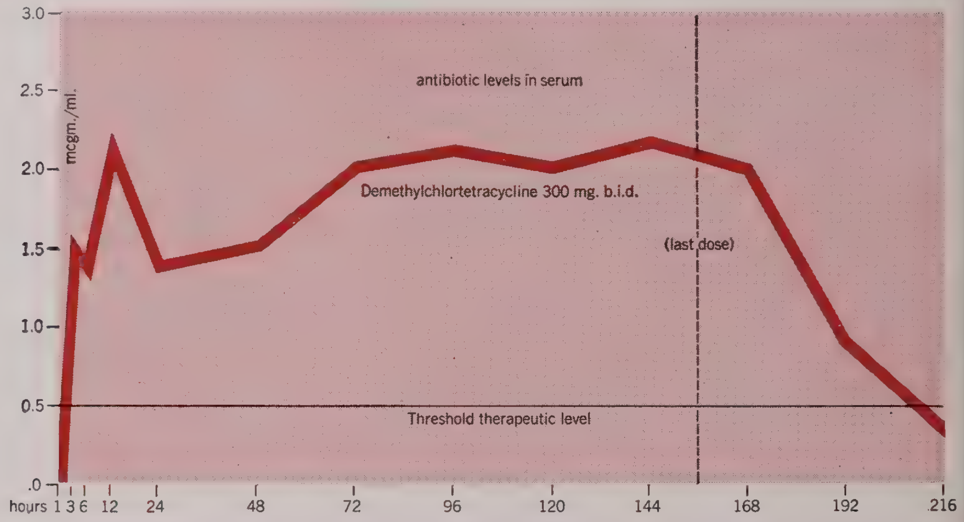

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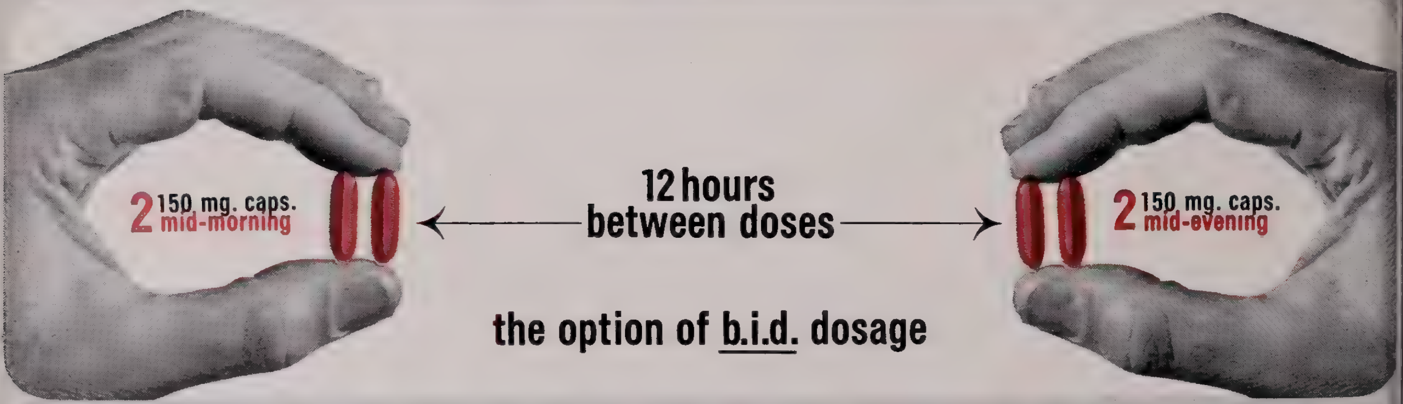

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President's Letter

Dr. James Z. Appel, the President of the American Medical Association, has recommended close and cooperative efforts by the physicians of the United States in working with those Government officials charged with implementing the Federal program of medical care.

This attitude, as could be expected, has been challenged by individual physicians and by some physician organizations. In reading Dr. Appel's reports both to the public and to various medical groups and associations, and in hearing Dr. Appel speak, the reasonableness of this recommendation becomes apparent. Provision of medical care for certain specified groups of Americans is now law, without constitutional challenge to date, and in consequence, must be obeyed. No law is ever implemented as it is written, however, and it is in the area of the development of regulations under which the law is enforced, that cooperative efforts can be a defense in the hands of those who are to be governed. It is in this area of the framework of developing regulations that sincere and dedicated physicians have been and are continuing to meet as technical advisory committees to administrators of the program.

Concession, in response to the demands of a law, may involve physicians in situations far from desirable, but is possible without compromise. To accept undesirable situations without strenuous efforts at improvement *is* compromise and should be wholeheartedly opposed by all physicians. That physician opposition to a legislative approach to the provision of medical care for self-sufficient Americans has been vigorous and vocal is now history. The later inclusion by law of those individuals originally recommended by the American Medical Association on the basis of medical indigency has in no way diminished medical opposition to care for those competent to care for themselves. Opposition to the law, however, should not be the present basis for criticism directed at those charged with the responsibility of best identifying what efforts, applied in what areas, will have the maximum results in providing, as physicians have always provided, optimum medical care under conditions physicians can modify, accept, and live with.

Our recent failure to convince our patients that the regimentation of physicians is in effect the regimentation of them as well, can never be the reasonable basis for any efforts at retaliation by obstruction or any other means. The integrity of our position can only be maintained by continuing efforts to support the rights of doctors as individuals and to develop new, and protect old, policies of benefit to patients, as individuals, as well.

To accept anything less *is* compromise. To continue the cooperative efforts Dr. Appel advises, and the American Medical Association is pursuing as a program developed and encouraged by the thoughtful deliberations of our elected physician-representation in the American Medical Association, is to serve medicine and our patients in the best medical tradition, in new and unusual circumstances.

RP Buckley M.D.

R. P. Buckley, M.D.
President
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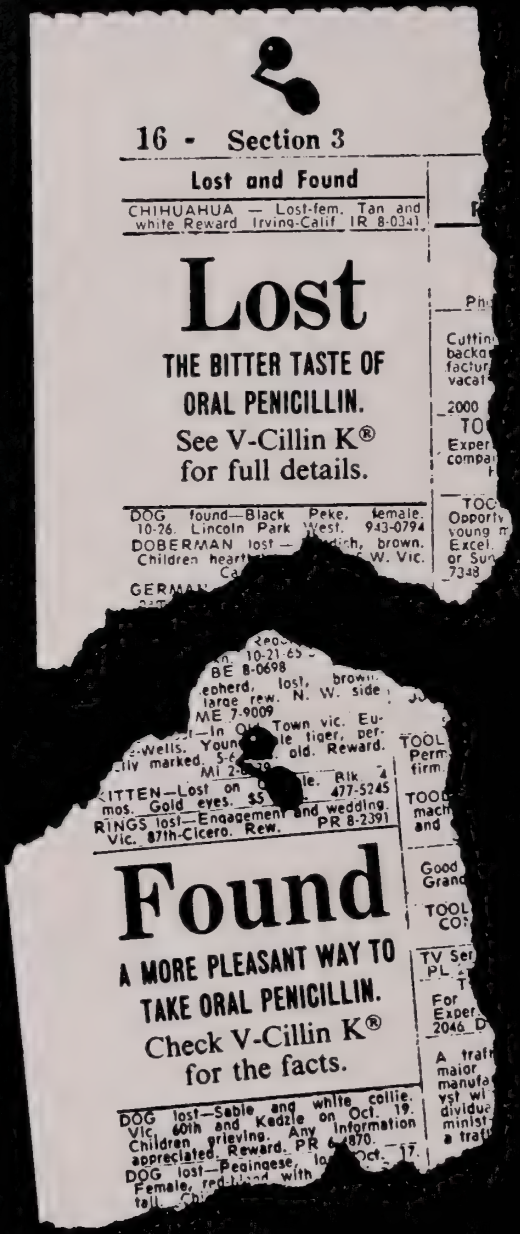

16 - Section 3

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ME 7-9009
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Wells. Youn le tiger, per-
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Mi 2-
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Demonstration of Tuberculosis in the Human Bone Marrow

Improved Technique

EMIL MARO SCHLEICHER, Ph.D.*
Minneapolis, Minnesota

"WE CANNOT afford to be satisfied with the present rate of progress against tuberculosis. The number of active cases reported each year is declining too slowly." This challenging remark cited by Tempel[1] and attributed to the Surgeon General, Luther L. Terry, U.S. Public Health Service, reveals clearly that tuberculosis is still a formidable disease.

That tuberculosis may be demonstrated by means of biopsy of the bone marrow organ has been amply demonstrated;[2-10] yet this helpful tool is not as widely employed as it should be. The reason for the lack of interest in this mode of case finding is the difficulties of evaluating the numerous marrow biopsy methods in use today and the greatly divergent results obtained by investigators.

It is the purpose of this communication to present an improved marrow-biopsy technique which, in our hands, is yielding uniform results. The technique is a modification of one previously reported;[3] the method is based on the knowledge that tubercles are within "marrow units" only.[2,3]

Marrow Units

The term "marrow units" is synonymous with marrow fragments, particles, and Markbröckel. They are minute masses of vital marrow tissue obtained by aspiration from the trabeculated areas of the bones.[11] Their consistency is jelly-like; thus they are very labile. Their color is light gray to red, and their diameter is 0.5 to 1 mm., with the larger ones predominating. In general they are lighter than the specific gravity of formol-saline fixing fluid, which is 1.010. Some eighty to one hundred fifty marrow units are contained in a 10-ml. sample when physiologic conditions prevail.

In disease the consistency, color, size, quantity, and specific gravity may be altered, as a result of changes in the functional state of the marrow organ, the cellular composition of individual marrow units, and modification of the trabecular framework in the spaces of which they are cast. Thus the size of the marrow units may be 0.1 to 4 mm., and few to more than a thousand may be present in a sample. All may be of the floating, heavy, or intermediate type, and again all three types may be present in a sample. These gross changes suggest that marrow units are anatomical entities.

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*Director Hematology Section, Department of Pathology and Clinical Laboratories St. Barnabas Hospital, Minneapolis.

Aspiration Sites

Sternum

The preferred site in the adult and young adult is the mid-line of the body of the sternum at the level of the second intercostal space (Figure 1).

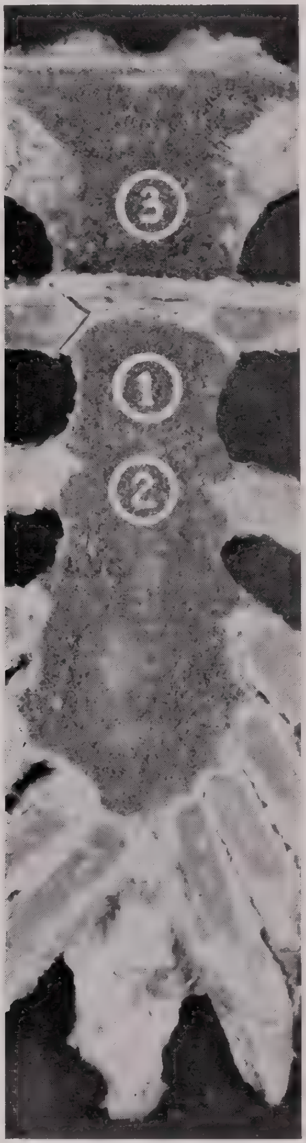

Fig. 1 — Longitudinal section of an average sternum of an adult. The preferred aspiration site is shown by the circle enclosing the number "1," the alternate areas by the circles "2" and "3."

The sternal area "2", manubrium area "3", anterior superior spine of the iliac crest, and spinous processes of the lumbar vertebrae are alternate sites, used only when multiple aspirations are necessary.

Manubrium

This bone is preferred as the aspiration site in children two to ten years of age.

Tibia

In children under the age of two years the preferred site is the tibia bone just below and slightly medial to the tibial tuberosity. The posterior iliac spine is the alternate site.

The reason for preferring the above cited bones for obtaining a marrow sample is based on studies of the distribution of functional marrow in these bones wherein Schleicher,[11] Denst and Mulligan,[12] and Hashimoto[13] have observed the presence of adequate amounts of red marrow. Hashimoto et al.[14] found a higher incidence of tuberculosis in the sternal-vertebral marrow than in other bones.

Aspiration Technique

When the aspiration instrument is properly situated in the medullary cavity, a 20-ml. sterile syringe is attached, its inside moistened with a sterile heparin solution (sodium heparin 1000 units, 1 ml., sterile physiologic sodium chloride solution, 9 ml.). The plunger is slowly withdrawn to the 2-ml. mark, and when marrow substance enters the barrel the plunger is rapidly pulled to the 20-ml. division and held there until 5 to 10 ml. of marrow substance is obtained. The specimen is immediately expelled into a paraffin coated glass vial and after the stopper is secured the vial is inverted several times to assure a uniform distribution of the heparin solution.

Standard Marrow Sample

It is routine in our institution to aspirate a marrow sample of 10 ml. from the adult and young adult patient, and 5 ml. from children. These amounts are not excessive considering that tuberculosis is not necessarily diffusely disseminated in the marrow organ, and that tubercles are within marrow units, with their quantity varying considerably in a random sample.

Processing of the Sample

Because of the physical character of the marrow units the sample must be immediately processed.* It is of the utmost importance that the separation of the marrow units from the blood and free fat part of the sample be carried out meticulously. To keep trauma and loss of marrow units at a minimum, a funnel valve assembly is employed (Figure 2). As the valve can be adjusted so that marrow units of 0.1 ml. are retained in the funnel, this mechanical aid is more efficient than the apparatus previously described.[15]

Method

1. The valve of the apparatus is adjusted to a filtration rate of 60 drops per minute of cold formol-saline fixing fluid (neutral formaldehyde, 10 ml., cold physiologic sodium chloride solution, 90 ml.) made up before use. The heparinized marrow sample is poured in the funnel, which is kept half filled with cold fixing fluid by continuous additions. The marrow units become exposed to clean fixing fluid while the blood and free fat part filter off and thus harden uniformly and rapidly. Marrow units sticking to the funnel wall or the valve stem are washed back into the fixing fluid.

2. When the fixing fluid is clear, the marrow units and the fluid are flushed into a glass beaker and allowed to harden at room temperature for one to two hours to assure complete fixation.

3. The sample is returned to the apparatus and the fixing fluid allowed to filter off.

4. Alcohol (80 per cent) is poured over the marrow units and the sample collected in a round or square glass dish with a grid. The marrow units may remain in the alcohol from one-half to one hour to overnight.

At this step the size range and quantity of the marrow units are determined. A plastic metric ruler is placed under the dish, or a few large and small marrow units are picked up with a medicine dropper and deposited on a metric scale and their size recorded. The marrow units are then tallied and the proportion of large to small is noted.

5. The alcohol is decanted and the marrow units exposed to alcohol (95 per cent) for one-half to one hour.

6. The alcohol is pipetted off and the marrow units exposed to two changes of acetone for one-half hour each.

7. The marrow units and acetone are transferred into a paper container (two

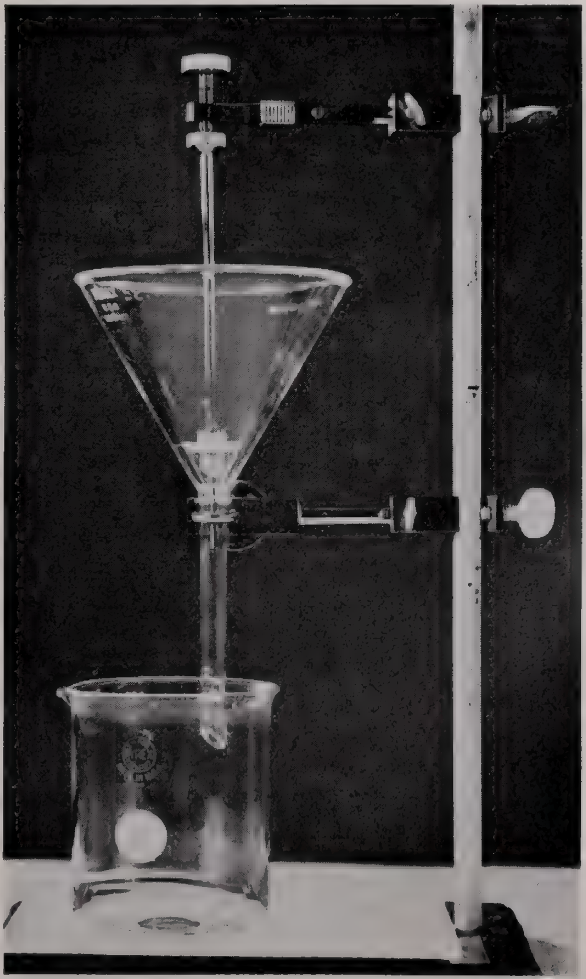

Fig. 2 — Funnel valve assembly** for the separation of marrow units from the admixture of blood and free fat part of the marrow sample.

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*If a marrow sample cannot be processed immediately after removal the aspirate may be poured into cold formol-saline fixing fluid, the quantity of which should be ten times that of the sample. To assure proper fixation of the marrow units, the sample should be well dispersed in the fluid with a glass rod.

**Distributed by Aloe Scientific, St. Louis, Mo.

one-ounce No. 101 Dixie paper cups one inside the other) and the acetone pipetted off.

8. Melted paraffin (50-52°C.) is rapidly poured over the marrow units and well dispersed through the paraffin with a warm glass rod.

9. The sample is placed for one hour in an oven set at 58 to 60°C.

10. The paraffin is replaced by melted paraffin (56-58°C.) and the specimen returned to the oven for one-half to one hour.

11. The marrow units are then blocked in a square or rectangular tissue area. While blocking, care is taken to approximate the marrow units as closely as possible and in such a manner that the greater number lie on the same plane. Two or more blocks are made when the quantity of marrow units is very large. Serial sections are cut at 5 micra, mounted, and stained according to methods published elsewhere.[16,17]

Serial Sections

The number of serial sections to be prepared and examined is based on the diameter of the greater number of marrow units. Assume the latter is 1 mm., when serially cut at 5 micra, 200 sections are obtained. Since a single tubercle in general replaces one fourth to three fourths of the marrow unit parenchyma, and several tubercles are irregularly scattered through a marrow unit, 50 to 100 serial sections reveal the lesion.

Reliability of the Serial Section

The marrow sample from one of the patients on whom marrow biopsy was done for diagnosis contained 1580 marrow units with an average thickness of about 1 mm. Because of the large quantity of marrow units three blocks were made at the time of embedding. From each of these blocks 50 serial sections (250 micra) were cut. In only one of the three sets of serial sections was there a marrow unit with a tubercle, which appeared first in section 23, and the only two bacilli in section 25. The singularity of the tubercle was demonstrated by completely serial sectioning all three blocks, and the sparsity of bacilli by staining the sections showing part of the tubercle with the Ziehl-Neelsen method.

Figure 3 shows part of a serial section of the 1580 marrow unit aggregate and the single marrow unit harboring the tubercle. In contrast Figure 4 presents a heavily infected marrow from one of the patients with generalized miliary tuberculosis. The sample contained 34 marrow units, eleven of which harbored one to several tubercles. Acid-fast

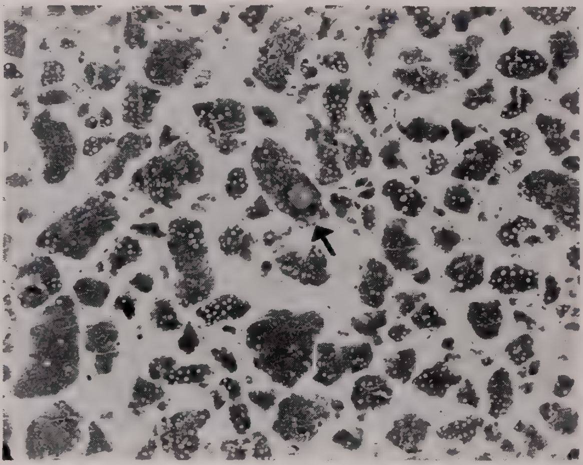

Fig. 3 — Part of a serial section of the 1580 marrow unit aggregate of one of the patients on whom marrow biopsy was done for diagnosis. Arrow points to the only marrow unit with a tubercle. Acid-fast bacilli could be demonstrated in only one section. Photomicrograph x 50. Hematoxylin-Eosin stain.

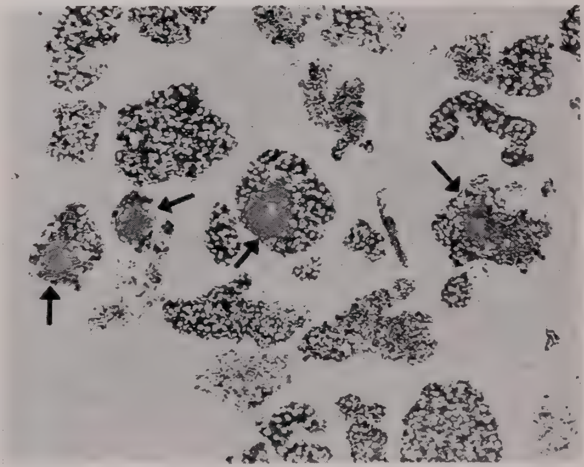

Fig. 4 — Part of a serial section of the 34 marrow unit aggregate of one of the patients with generalized miliary tuberculosis. Arrows point to marrow units with a tubercle. Eleven marrow units harbored tubercles but acid-fast bacilli were present in only seven tubercles. Photomicrograph x 125. Hematoxylin-Eosin stain.

bacilli were present in seven tubercles only, and in more than one serial section bacilli could be demonstrated. The tubercles first appeared in serial section 3.

Discussion

It is evident that for the demonstration of tubercles in the human bone marrow a biopsy technique is to be employed which yields uniform and reliable results. The technique must conform to the anatomy of the marrow organ in the trabeculated areas of the bones and allow obtaining a quantity of *marrow units* representative of the functional state of the organ. Emery and Gibbs[8] point out that "the probability of finding tubercles in the marrow will depend largely on the volume of tissue examined." They obtained a marrow sample of 0.1 ml. from forty-four children dying with generalized miliary tuberculosis, noting tubercles in thirteen specimens. These investigators saw tubercles only once in the routine single section made from the thirteen positive samples, thus pointing up the need of examining a large number of sections. Pease[6] procured a 2-ml. marrow specimen from each of fifty-six tuberculous patients, surveying 12 to 20 serial sections per slide, and found tubercles in nineteen samples. It is noteworthy that she saw tubercles in the marrow sample of four patients with miliary tuberculosis. Gormsen[5] aspirated 0.5 ml. and less of marrow from thirty-one patients with nonterminal tuberculosis mostly of the pulmonary type. He saw no tubercles in two to three sections made from the clot. Since marrow units tend to be scattered through the coagulum, failure to section the entire clot may leave infected ones in the uncut portion. Mooma and Alt[9] procured 1 ml. of marrow substance from eleven patients with far-advanced pulmonary tuberculosis. They used one half of the sample for histologic preparations. Moomaw and Alt expelled the sample on a glass plate transferring the marrow units with a dissecting needle to a filter paper. Trauma and loss of marrow units are inevitable. They examined eight sections from each marrow specimen noting tubercles in only one sample. The different results reflect clearly a direct relationship between the amount of marrow substance obtained and the mode of processing the sample.

Results with the Improved Technique

The results achieved with the marrow biopsy technique presented in this communication are shown in Table 1. Box I shows

TABLE I

Quantity and Frequency of Marrow Units with Tubercles Per Marrow Sample of Thirty-four Selected Patients with Known Tuberculosis, and of Seventeen Patients on Whom Marrow Biopsy was Done for Diagnosis

Diagnosis	Number of Patients	Marrow Pos.	Marrow Neg.	Amount Aspirated ml.	Range of Marrow Units Per Positive Sample	Range of Marrow Units with Tubercles	Range of Section Number when Tubercle First Seen	Positive Cases %
I Generalized Miliary Tuberculosis	17	17	—	5-10	34-253	11-27	3-8	100
II Active pulm. tuberculosis	10	6	4	10	72-800	2-8	42-64	64.7
Arrested pulm. tuberculosis	4	2	2	10	350-984	1-5	20-33	
Tuberculosis of kidney	1	1	—	10	41	3	27	
Tuberculosis of intestines	1	1	—	10	228	5	39	
Tuberculosis of meninges	1	1	—	10	147	7	48	
III Marrow biopsy for diagnosis	17*	6	11	10	80-1580	1-9	23-44	35.2

*Not previously reported

that in generalized miliary tuberculosis the marrow organ appears to be invariably affected. This is in accord with the findings of Chapman and Whorton,[18] and Hashimoto et al.,[14] who noted tubercles in all autopsy marrow specimens from patients with generalized miliary tuberculosis.

The data in Box II reveal a greater number of positive samples obtained from patients with other forms of tuberculosis than are reported by the above cited investigators.

Although the primary focus of the disease could not be established in the six positive cases out of the seventeen patients on whom marrow biopsy was done for diagnosis shown in Box III, the detection of tuberculosis in these individuals and concomitant demonstration of acid-fast bacilli in the tubercles are unequivocal proof of the value of bone marrow biopsy in case finding during life.

Conclusion

An improved marrow-biopsy technique for the demonstration of tuberculosis during life is presented. The technique is based on the knowledge that tubercles are within *marrow units*.

It is important that the admixture of blood and free fat be separated from the sample and that trauma and loss of *marrow units* be kept to a minimum. Table 1 shows that the incidence of tuberculosis of the human bone marrow is greater than has been noted by other investigators.

Acknowledgment

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Derivatively Speaking

Cadaver — from Latin cadere (to fall)

Arteriovenous Fistula

Involving
the
Renal
Vessels

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ARTERIOVENOUS FISTULA involving the renal vessels with an intact kidney is a rare entity. Of 34 such cases reported in the medical literature all but one occurred between the renal artery and the renal vein. The exception was a patient who, following an abdominal stab wound, developed a fistula between the aorta and the left renal vein. The case to be presented here will, therefore, be the second reported case of aorticorenal-vein communication with the fistula originating from the anterior wall of the aorta adjacent to the origin of the superior mesenteric artery. In spite of this critical location, the fistula was transected successfully with the preservation of a normally functioning left kidney. The rarity of the lesion, the technique utilized, and a review of the literature form the basis for this report.

Case Report

A 23-year-old male sustained a bullet wound of the abdomen on April 20, 1963, the bullet having

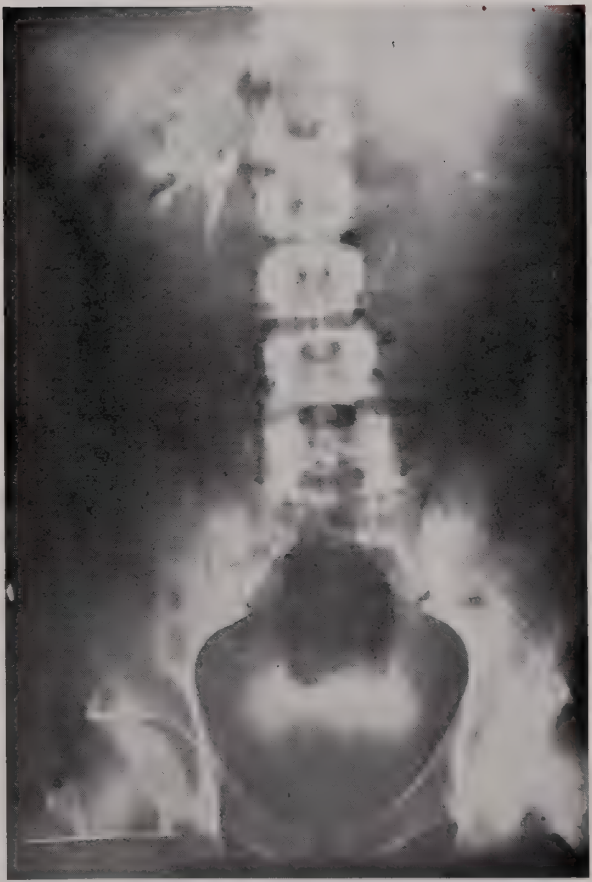

Fig. 1 — Failure of prompt excretion of the left kidney prior to surgery. In later film (L) kidney visualized better.

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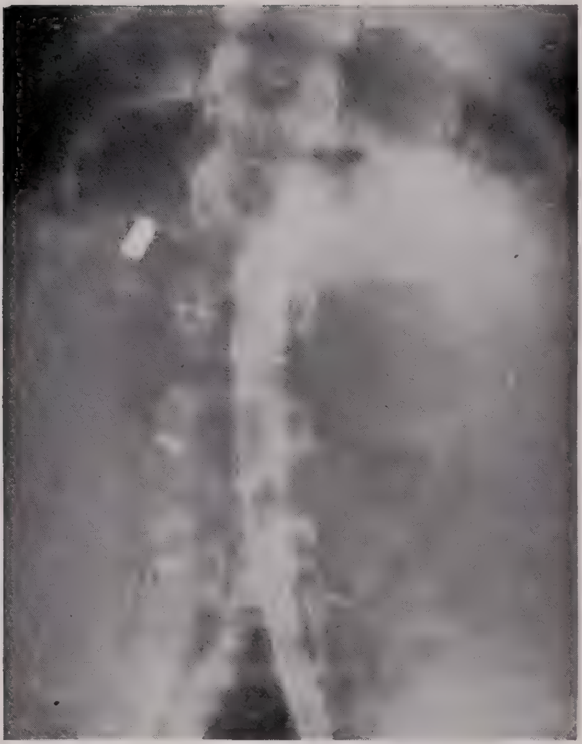

Fig. 2 — Aortogram showing opacified and distended left renal vein. Increased density overlying the aorta represents the site of the fistula.

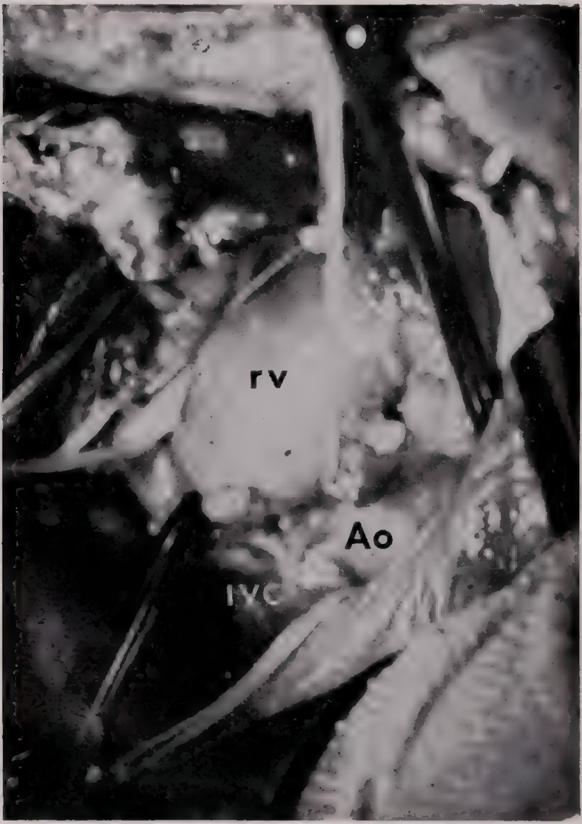

Fig. 3 — Markedly enlarged left renal vein (r. v.) Ao (Aorta). IVC (Inferior vena cava).

entered the left upper quadrant and lodged in the posterior abdominal wall. Immediate exploration revealed perforations in the stomach, pancreas, and the second portion of the duodenum, together with a large hematoma presumably from a lacerated lumbar artery. Two months after repair of these perforations he was readmitted with a diagnosis of partial intestinal obstruction which was treated conservatively.

Symptoms

His intermittent abdominal pain continued, however, and became further complicated by the appearance of a mass in the left upper quadrant of the abdomen. The size of the mass varied from time to time; but the mass itself never disappeared. On his third admission one year after the initial injury pertinent physical findings included a slightly tender, pulsatile mass, 8 centimeters in diameter, in the left upper quadrant. A continuous bruit was best heard in the mid back, but was also heard over the mass itself. His heart size was normal; his blood pressure was 130/60. Intravenous pyelogram showed delayed excretion of the dye from the left kidney (Fig. 1). A retrograde femoral arteriogram confirmed the presence of an arteriovenous fistula between the aorta and the left renal vein (Fig. 2). The left upper quadrant mass was felt to be unrelated to the fistula and was thought to be a pancreatic pseudocyst.

Findings at Operation

Surgery was performed on May 4, 1964. A large pseudocyst of the pancreas was found. In addition, an arteriovenous fistula was identified between the anterior wall of the aorta and the posterior wall of the left renal vein (Fig. 3). The left renal vein measured approximately 2 inches in diameter and demonstrated a continuous thrill which transmitted into the inferior vena cava. Complete dissection of the suspected area led to the localization of the fistula, which measured 1 cm. in external diameter and ½ cm. in length. It originated from the anterior wall of the abdominal aorta immediately adjacent to the origin of the superior mesenteric artery and terminated in the posterior aspect of the left renal vein (Fig. 4). Extensive retroperitoneal and periaortic fibrosis secondary to previous peritonitis and exploration contributed to difficulty in identifying the renal artery. Cord tapes were then placed around the aorta at the level of the diaphragm, the superior mesenteric artery, and the left renal vein on both sides of the fistula. The fistula was clamped at its origin by a partially occluding aortic clamp, while the left renal vein was clamped on both sides of the fistula, which was then transected. To avoid left renal congestion during venous occlusion, and without identification of the renal artery, the abdominal aorta was clamped at the level of the diaphragm. The defect in the vein measuring 1 cm. in diameter was closed using fine vascular suture. The proximal divided end of the fistula was then sutured and the partially occluding aortic clamp removed. The thrill disappeared and the left renal vein decreased markedly in size (Fig. 5). A drainage procedure was carried out for the pseudocyst of the pancreas. The patient had an uneventful recovery and left the hospital one week postoperatively. A postoperative intravenous pyelogram before discharge was normal (Fig. 6).

Discussion

The majority of the fistulae involving renal vessels have been described in the last decade, indicating a recent increasing awareness of this entity. The first case was reported by Varela in 1928.[41] Since then, at least 33 more cases have been added. The ages of the patients ranged between three and 70 years, there being no difference in sex distribution.

Etiology

As demonstrated in Table 1, of 34 cases with known etiology, 18 were considered to be congenital. These were usually multiple, arising from one or many branches of the renal artery. Pre-existing congenital aneurysms have been considered as the primary lesions in this group. The remaining cases were due to trauma, malignant infiltration, or infection. Penetrating wounds constituted the commonest cause in the traumatic group (nine cases). Two cases were recorded as due to surgical procedures. In all of the traumatic group the fistula was single and involved the main portion of the renal vessels, the majority the left renal vessels.

There were five fistulae due to malignant infiltration of the artery, which eroded into the vein establishing a communication. Two patients developed a fistula due to infection:

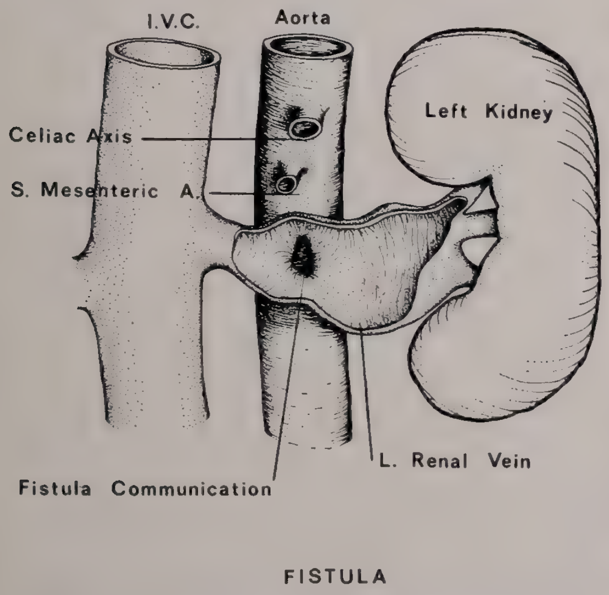

Fig. 4 — Diagram showing the location of the fistula and the dilated left renal vein.

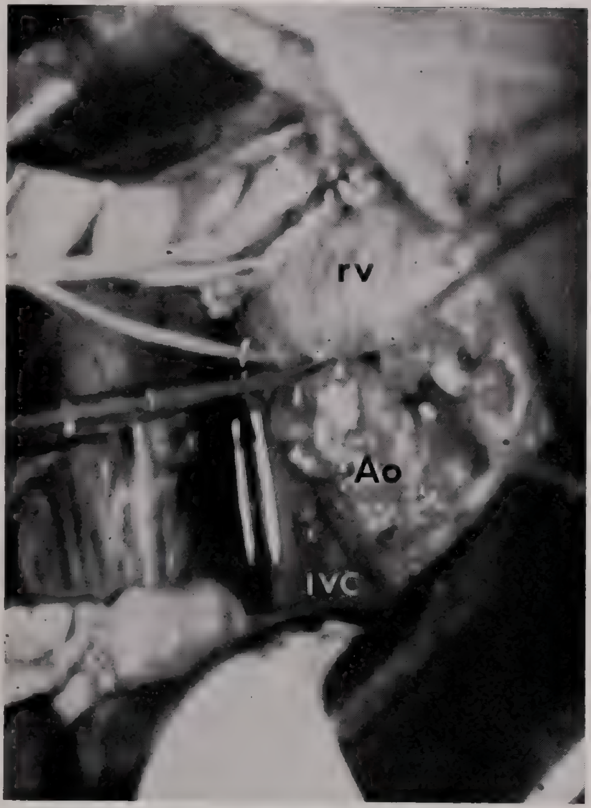

Fig. 5 — After clamping the fistula between the aorta and the renal vein, the latter decreased significantly in size (rv-renal vein). Ao (aorta) IVC (inferior vena cava).

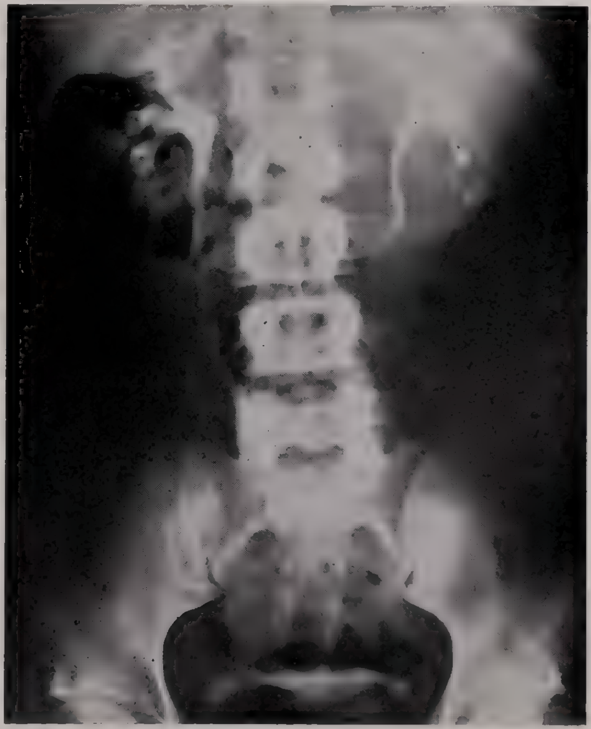

Fig. 6 — Simultaneous and equal excretion of the dye by both kidneys six days after closure of the fistula.

one secondary to subacute bacterial endocarditis, and the other due to an abscess formation.

TABLE 1
Etiology of Renal Arteriovenous Fistulae

1. Congenital	18 cases
2. Acquired	
A. Trauma	10 cases
B. Carcinoma	5 cases
C. Infection	2 cases

Clinical Symptoms

The presenting symptoms (Table 2) included fatigue, abdominal pain, palpable mass, flank pain with shock, peripheral edema, fever, and renal colic, with headache, dyspnea and hematuria constituting the most frequent original complaints. In general, most of the symptoms were those resulting from hypertension or congestive heart failure. Six patients experienced gross hematuria, in four of whom it was congenital. A continuous bruit in the flank was present in 24 cases. Evidence of congestive heart failure was reported in 20 cases regardless of the etiology. Hypertension ranked third in frequency (14 cases). Congestive heart failure was associated with hypertension in 10 cases. Wide pulse pressure was present in three cases, two with congestive heart failure. The remaining patients had normal blood pressure and complaints unrelated to the cardiovascular system, as in our case where the presenting symptoms were an abdominal mass in the left upper quadrant associated with pain.

Systemic and Local Effects

The effect of an arteriovenous fistula involving the renal vessels may be divided into two categories: systemic and local. The systemic effects are in general similar to those of peripheral arteriovenous fistula defined by Holman,[16,17] with the exception of the elevated blood pressure. The local effects on the tissues distal to the fistula are also similar. Epstein[11] summarizes the local renal effects as follows: decreased pulse pressure, ischemic changes, lowering of the renal plasma flow due to renal vasoconstriction, reduced glomerular filtration rate, and decreased chloride and water secretion. In the light of these observations it has been suggested that hypertension associated with arteriovenous fistula of the renal vessels may represent a Goldblatt phenomenon. However, experimentally created renal arteriovenous fistula in dogs, by Lasher and Glenn,[23] produced a mild and inconsistent hypertension. Regardless of the exact pathophysiology it is of special interest that of 19 cases of renal arteriovenous fistula associated with hypertension, 17 became normotensive following a nephrectomy.

Diagnosis

Clinical diagnosis of an arteriovenous fis-

TABLE 2
Main Symptoms and Signs of Renal Arteriovenous Fistulae

	Congenital	Trauma	Carcinoma	Infection
1. Continuous bruit	9	8	5	2
2. Congestive heart failure	11	4	3	2
3. Hypertension	8	6	3	
4. Wide pulse pressure	2	1		
5. Hematuria	4	1	1	1
6. Renal colic	1			

TABLE 3
Treatment

	Congenital	Trauma	Ca	Infection
1. Nephrectomy	14	8	5	2
2. Heminephrectomy	2			
3. Repair of Fistula		2		
4. No Treatment	1			
5. No Mention of Rx		1		

tula based on the presence of a continuous bruit is confirmed by aortography. The classical picture is that of slightly opacified space overlying a well opacified, dilated and tortuous renal artery with early visualization of the inferior vena cava. Increased oxygen saturation of the renal vein blood obtained by means of a catheter introduced into the inferior vena cava is also diagnostic. The intravenous pyelogram shows some degree of abnormality from delayed to poor visualization or abnormal appearance of the calyces due to the compression by the sacular renal vein.

Treatment

Of the 34 cases reported, 32 underwent surgery (Table 3). Procedure consisted of nephrectomy in 29, heminephrectomy in two and transection of the fistula and preservation of the kidney in only one. Hypertension and congestive heart failure were relieved in 27 out of 29 patients. Two improved, but the blood pressure remained elevated; one showed no improvement, and one died. The ideal treatment is transection of the fistula with preservation of the kidney. Of the entire group in only one was this accomplished. It was achieved in the patient with a fistula between the aorta and the renal vein, similar to the case under discussion.

Summary

In a patient with traumatic arteriovenous fistula between the left renal vein and the aorta the fistula was successfully transected, and the kidney was preserved. A review of the literature disclosed 34 previously reported cases of renal arteriovenous fistula with only one aorticorenal vein fistula. Symptoms of congestive heart failure and hypertension were the leading complaints with hematuria being the common symptom in the congenital group. Hypertension has been related to the Goldblatt phenomenon.* Treatment has usually been nephrectomy with alleviation of hypertension in all but two cases. The involved kidney was preserved in only two instances. The exceptions were the patients with traumatic aorticorenal vein fistula.

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*See Test Your Word Score Page 271.

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11-42 May be secured from the author or the reprints.

Andromachus

A physician of Crete who became body physician to the Emperor Nero. He invented a famous medical compound called "Theriacum Andromachi."

Sulfonamide-Resistant

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SULFONAMIDE-RESISTANT meningococci caused an outbreak of meningitis among recruits at the San Diego Naval Training Center in March, 1963.[1] Since that time, sulfonamide resistant Group B (Type II) Neisseria meningitidis has been observed with increasing frequency in both the military and civilian population. Eickhoff and Finland[2] reviewed the antibiotic sensitivity of meningococcal strains isolated from carriers and found only one isolate highly resistant to sulfadiazine.

During November of 1964, we studied meningococci isolated from the blood and spinal fluid of four children with cerebrospinal meningitis in the Bacteriology Laboratory at Hennepin County General Hospital. A Group C (Type IIa) strain of Neisseria meningitidis cultured from one of the patients was found to be highly resistant to sulfonamide drugs. The purpose of this communication is to alert the community to the existence of sulfonamide-resistant Group C meningococci in Minneapolis and to propose laboratory methods by which this problem may be studied.

Materials and Methods

The use of disc diffusion methods in evaluating micro-organism susceptibility to sulfonamides has been highly unsatisfactory. The reason is twofold. Many types of media contain peptones which inhibit the activity of the sulfonamides. In addition, the size of the zone of inhibition about a sulfonamide disc is inversely related to the number of organisms innoculated. Standardization of inoculum and use of Mueller-Hinton agar‡ partially compensate for these variables.

One solution to this problem is to use Mueller-Hinton agar plates with twofold dilutions of sulfonamide incorporated in the media. Plate dilution techniques, however, require vast numbers of plates with varying concentrations of antimicrobial agents and are laborious unless an inocula-replicating method is employed. Moreover, tests done on different media with different methods of plate innoculation cannot be directly compared.

A rapid and convenient quantitative tube dilution technique by which meningococcal susceptibility to sulfonamides may be compared is urgently needed. Wilson's[3] tube dilution technique, developed for study of beta hemolytic streptococci, appears to be adaptable to the evaluation of meningococcal sensitivities in our preliminary studies. Consider-

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Neisseria Meningitidis

• in
• Minneapolis*

able experience with this method has been accrued at the University of Minnesota Hospitals while studying sulfonamide sensitivity of gram-negative isolates from genitourinary tract infections.

Bacterial isolates were maintained on sheep-blood agar and subcultured biweekly. Initial sensitivity testing was performed on Mueller-Hinton agar with discs containing sulfisoxazole .25 mg. (B.B.L.).

TABLE I
Case Material

Case	Presenting Symptoms	Laboratory Blood	Lumbar Puncture	Cultures	Sensitivities	Rx	Result
Case #1 D. S. (age 3 yr.)	Anorexia, lassitude, leg pains	WBC-51,000/MM^3 55% PMN	WBC-3460/MM^3 68% PMN Protein-228mg% Sugar-78mg% Smear-gram neg. diplococci	Throat, Blood and CSF-N. Meningitidis Group B (Type II)	Highly sensitive to sulfadiazine	Penicillin $12^6/M^2/10d$ Sulfisoxazole 150mg/kg/10d Chloromycetin 100mg/kg/2d	No residual
Case #2 C. B. (age 4 yr.)	Stiff neck, lethargy	WBC-23,400/MM^3 95% PMN	WBC-5100/MM^3 PMN-100% Protein-430mg% Smear-gram neg. diplococci	CSF-N. Meningitidis Group B (Type II)	Highly sensitive to sulfadiazine	Penicillin $12^6/M^2/10d$ Sulfisoxazole 150mg/kg/10d Chloromycetin 100mg/kg/2d	No residual
Case #3 G. H. (age 6 mo.)	Fever, lethargy, respiratory arrest	WBC-14,500 60% PMN	WBC-3775 PMN-98% Protein-234mg% Sugar-9mg% Smear-gram neg. diplococci	Throat, petechiae Blood, CSF-N. Meningitidis Group C (Type IIA)	Resistant at 25mg% by tube dilution to sulfadiazine	Penicillin $12^6/M^2/15d$ Gantrism 150mg/kg/5d Chloromycetin 100mg/kg/2d	Slow recovery No residual
Case #4 K. W. (age 3 yr.)	Fever, stiff neck	WBC-24,300 55% PMN	WBC-17,500 PMN-98% Protein-340mg% Sugar-15mg% Smear-gram neg. diplococci	CSF and blood N. Meningitidis Group B (Type II)	Highly sensitive to sulfadiazine	Penicillin $12^6/M^2/10d$ Sulfisoxazole 150/mg/10d Chloromycetin 100mg/kg/2d	Died at 48 hours

The tube dilution method used was a modification of that proposed by Wilson.[3] A working solution of sulfisoxazole diethanolamine containing 10 mg./ml. was made up from a stock solution with a concentration of 4 grams/10 ml. obtained from the hospital pharmacy. By means of sterile technique, 4.4 ml. of working solution containing 44 mg. of sulfisoxazole diethanolamine was added to a flask containing 37.0 ml. of S R Medium Base (Difco*). After 30 minutes in a 42 C. water bath, the flask was permitted to cool at room temperature. Horse serum, 3.0 ml., was then added to make a total of 44.4 ml. of solution. The final concentration of sulfisoxazole diethanolamine was 100 mg./100 ml. Thereafter, 18.5 ml. S. R. Medium Base was delivered into each of nine additional flasks; horse serum, 1.5 ml., was added to each to make a total of 20.0 ml. of solution. By transferring 20.0 ml. of the sulfisoxazole solution to a flask containing 20.0 ml. of growth medium, and continuing serial dilutions in this manner to the ninth flask, twofold dilutions ranging from 50.0 to 0.39 mg./100 ml. were obtained; the tenth flask served as a control medium. For actual testing, 2 ml. volumes of each dilution (nine tubes) and a growth control tube were used.

A heavy inoculum of Neisseria meningitidis was transferred from sheep-blood agar and grown in pure culture in tryptose-phosphate broth. After 24 to 48 hours, the growth in the broth was seeded into 20.0 ml. of S R diluent (Difco). Two strains failed to show adequate growth in tryptose-phosphate broth after 48 hours; however, an appropriate inoculum was obtained by substituting brain-heart-infusion broth as the growth medium. Representative pour plates were done to assure an adequate inoculum in all instances. Each of nine sulfisoxazole-containing tubes and the growth control tube were inoculated with the organism suspended in one drop of S R diluent. The highest dilution showing no turbidity was the minimal inhibitory concentration (M.I.C.) of sulfisoxazole for a particular organism. The reproducibility of this method has been extensively evaluated in routine sulfisoxazole tube dilution testing performed at the University of Minnesota Hospitals.

The plate dilution method utilized in our laboratory was performed by incorporating twofold dilutions of sodium sulfadiazine into Mueller-Hinton agar plates. A stock solution of sodium sulfadiazine containing 0.25 gm./ml. was obtained from the Hennepin County General Hospital pharmacy. A working solution of 25 mg./ml. was made up by adding 9.0 ml. of saline to 1.0 ml. of stock solution in a sterile test tube. Exactly 5.0 ml. of sterile saline was then delivered into each of nine additional test tubes. By transferring 5.0 ml. of sulfadiazine solution to each of the tubes in the series, twofold dilutions were obtained with a range of antibiotic concentration between 25.0 and 0.39 mg./ml. A volume of 0.1 ml. of each antibiotic concentration was then delivered into each of nine sterile petri dishes containing 9.9 ml. of Mueller-Hinton agar; the tenth petri dish containing only Mueller-Hinton agar was used as a growth control medium. In this study the range of antibiotic concentration in the Mueller-Hinton plates was from 25.0 to .39 mg./100 ml. The inoculum was taken from a Mueller-Hinton plate with a 3 mm. wire loop and hand streaked on the series of antibiotic containing plates. Adequate growth of each strain of Neisseria meningitidis was observed on the growth control media in each instance. The observed growth on each plate was graded qualitatively at 1 to 4+.

Sulfonamide blood level determinations were performed according to the method of Bratton and Marshall[4] and corrected for sulfisoxazole. The isolates were grouped by the tube agglutination technique performed at the Minnesota State Department of Health.

Case Reports

Neisseria meningitidis was isolated from the spinal fluid of four children with clinical meningitis. Brief summaries of the four case histories are presented below and in Table 1.

Case 1

A three-year-old Caucasian male was admitted to Hennepin County General Hospital on November 12, 1964, with a twenty-four hour history of fever, headache, nausea, and vomiting. He presented with a rectal temperature of 102 degrees F., photophobia, hyper-reflexia, and nuchal rigidity. Study of the peripheral blood revealed a white blood cell count of 55,000/mm^3. with 55% polvmorphonuclear leucocytes. A lumbar puncture showed a marked pleocytosis with a protein level of 228 mg%, and a sugar level of 78 mg%. The initial gram stain and subsequent cultures were positive for Group B (Type II) Neisseria meningitidis. The organism was sensitive to sulfisoxazole by the tube dilution technique and the plate dilution method at a level of 0.39%. The patient was successfully treated with penicillin and sulfisoxazole.

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Case 2

A four-year-old Caucasian female was admitted to Hennepin County General Hospital on November 30, 1964, with a two-day history of increasing lethargy, headache, and a stiff neck. She appeared semicomatose and had a rectal temperature of 102 degrees F., marked nuchal rigidity, generalized flaccidity, and a petechial rash extending over the trunk and extremities. The peripheral blood showed a white blood cell count of 23,000/mm.^{3} with a marked increase in neutrophils. A lumbar puncture disclosed milky fluid with a marked pleocytosis. The protein content was 430 mg%, and a gram stain was positive for gram-negative diplococci. The cerebrospinal fluid cultures grew out a Group B Type II Neisseria meningitidis, which exhibited marked sensitivity to sulfisoxazole at the 0.39 mg% level. The patient responded well to high doses of penicillin and sulfisoxazole.

Case 3

A six-month-old Caucasian male was admitted to Hennepin County General Hospital on November 10, 1964, with an eighteen-hour history of high fever and lethargy. En route to the hospital, the patient had a respiratory arrest and was admitted to the ward in a semicomatose state. Rectal temperature was 103 degrees F. Nuchal rigidity, papilledema, and a diffuse petechial skin rash were present. A white blood cell count was 14,500/mm.^{3} with 55% neutrophils. The initial lumbar puncture revealed a prominent pleocytosis. The spinal-fluid protein level was elevated to 234 mg%, and the sugar level decreased to 9 mg%. The gram smear showed large numbers of gram-negative diplococci. Cultures of the nasopharynx, spinal fluid, blood and petechiae grew out Group C Type IIA Neisseria meningitidis, which proved to be highly resistant to sulfisoxazole by the tube dilution and the plate dilution technique (Tables 2 and 3). The patient recovered slowly after a fourteen-day period of therapy with high doses of penicillin and sulfisoxazole. The father of this patient, a career army enlisted man, had been transferred to Minneapolis in October, 1964. On tracing his whereabouts during the preceding year, no exposure to epidemics of sulfonamide-resistant meningococcal disease could be demonstrated.

Case 4

A three-year-old Caucasian female was admitted to Hennepin County General Hospital on November 20, 1964, after two days of high fever and lethargy. On admission, a generalized petechial rash was apparent and the child was convulsing and semicomatose. Marked nuchal rigidity and papilledema were evident. After a respiratory arrest, she was placed on positive pressure respiration. Over the next two days her condition deteriorated and she expired. The initial white blood cell count was elevated to 24,300/mm^3. A lumbar puncture showed large numbers of gram-negative diplococci. The cloudy cerebrospinal fluid showed a striking pleocytosis with a protein level of 340 mg% and a sugar level of 15 mg%. The peripheral blood and spinal fluid cultures grew out Group B Type II Neisseria meningitidis with marked sensitivity to sulfisoxazole by the tube dilution and plate dilution methods. Autopsy findings confirmed the clinical impression of marked cerebral edema and meningeal inflammation.

Results

Sensitivity testing was done for both sulfadiazine and sulfisoxazole. The sulfadiazine sensitivity determinations by the Mueller-Hinton agar plate dilution method are presented in Table 2. Note that the Group C (Type IIa) meningococcus isolated from Case 3 shows significant resistance to sulfa-

TABLE 2
Sulfadiazine Sensitivity Determinations
Mueller-Hinton Agar Plate Dilution
Meningococcus Group

	B	B	C	B
	Case No.			
Sulfadiazine mg./100 ml.	1	2	3	4
0.39	2+	3+	4+	1+
0.78	—	—	4+	—
1.56	—	—	4+	—
3.12	—	—	3+	—
6.25	—	—	1+	—
12.50	—	—	—	—
25.00	—	—	—	—

TABLE 3
Sulfisoxazole Sensitivity Determinations
Wilson Tube Dilution Method
Meningococcus Group

	B	B	C	B
	Patient No.			
Sulfisoxazole mg./100 ml.	1	2	3	4
0.39	±	±	4+	±
0.78	—	—	4+	—
1.56	—	—	4+	—
3.12	—	—	4+	—
6.25	—	—	4+	—
12.50	—	—	3+	—
25.00	—	—	1+	—
50.00	—	—	—	—
100.00	—	—	—	—

diazine. The Group B (Type II) meningococci isolated from Cases 1, 2, and 4 uniformly show marked sensitivity to sulfadiazine. The four cerebrospinal fluid isolates were also tested for sensitivity to sulfisoxazole by the modified Wilson Tube Dilution Method. Table 3 shows that the Group C (Type IIa) isolate from Case 3 was resistant to 25 mg./100 ml. of sulfisoxazole, whereas the remaining Group B (Type II) isolates exhibited marked sensitivity. No significant difference was observed in parallel determinations with sulfadiazine and sulfisoxizole.

Group B (Type II) Neisseria meningitidis have been implicated in all previous epidemics caused by sulfonamide-resistant organisms. Thus far, no sulfonamide-resistant Group C (Type IIa) strains of Neisseria meningitidis have been reported from cases of clinical meningitis. It appears that the spectrum of resistant organisms is increasing to involve additional strains of meningococci.

Discussion

The treatment of meningococcal carriers with sulfadiazine was standardized in the classic studies of Schoenback and Phaer[5] in 1948. Recent military experience suggests that neither sulfadiazine nor penicillin G when given orally for a four-day period is effective in eradicating the carrier state.[1] The occurrence of fatal cases of meningococcal meningitis in this community requires us to re-evaluate our program of prophylaxis in meningococcal carriers. The efficacy of penicillin G in high dosage in eliminating the carrier state remains to be defined. There appears to be little doubt that penicillin G is an excellent adjunct to sulfadiazine in the treatment of active clinical cases of meningitis. In our studies, the resistant Group C (Type IIa) strain as well as the Group B isolates were highly sensitive to penicillin G. A satisfactory therapeutic effect was obtained by treating our patients with penicillin G and sulfisoxazole.

Summary

Bacterial isolates from four cases of meningococcal meningitis treated at Hennepin County General Hospital have been studied for resistance to sulfonamide drugs, and it was found that Group C (Type IIa) strain of Neisseria meningitidis, isolated from the blood and spinal fluid of one child, was highly resistant to sulfonamide. A modified Wilson Tube Dilution technique has been found to be an effective means of determining sensitivity to sulfisoxazole.

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Pliny on Birth Control

Pliny declared against abortive drugs as well as love charms, but cited one recipe for birth-control for the benefit of over-fecund women, consisting of a ligature of two little worms found in the body of a certain species of spider and bound on in deer-skin before sunrise. After a year the virtue of this charm expires.*

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*Thorndike, Lynn: A History of Magic and Experimental Science, Vol. 1, p. 94. The MacMillan Company, New York, 1923.

Conventional Scanning vs. Scintillation Camera

A Comparison for Evaluation of Brain Pathology

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A DETAILED comparison of results of organ visualization by conventional scanning to those obtained with the scintillation camera[1] is under way. This study includes all organs which may be visualized using selected radioisotopic preparations. Special attention is being given to short-lived radioactive materials which will permit improved resolution and decreased radiation exposure to patients despite administration of relatively larger amounts of these materials than are normally employed for conventional scanning. This is a preliminary report of studies performed with mice, a brain phantom, and of patients suspected of having brain tumors. Special consideration has been given to the use of 99m technetium in the form of pertechnetate[2] as an agent for brain studies, and comparison is made to results obtained with 197 mercury chlormerodrin. When possible, both agents are being used for camera and scan studies in individual patients.

Technical Considerations

99m technetium is obtained from a 99Mo-Tc generator.** These generators are now prepared so that the 99m technetium may be eluted by addition of pyrogen-free normal saline to the resin column. We find that more than 90 per cent of the technetium is removed in the first 10 milliliters of eluate with each daily milking. Yields of the technetium are within expected values (about 75 per cent of that calculated) with less than 0.1 per cent 99 molybdenum contamination. Daily samples have been assayed using both the 400-channel analyzer and liquid scintillation systems. Both methods show the expected decay constants for 99m-Tc and 99Mo. The energy spectrum as visualized from the analyzer unit is likewise as expected. Following sterilization by autoclave, the 99m-Tc is standardized by comparison to a known activity of 57-Cobalt.[3]

Experiments in which mice were given

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*From the Nuclear Medicine Clinic, University of Minnesota Hospitals.

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**Brookhaven National Laboratories, Upton, New York and Nuclear Consultants Corporation, St. Louis, Missouri.

100 microcuries of technetium by intravenous route and sacrificed at various times thereafter have shown that the 99m-Tc is initially handled very much like radioactive iodine. At one hour after administration the majority of the 99m-Tc removed from the blood stream is found in the salivary glands, thyroid, and stomach. The 99m-Tc concentration in these organs gradually increases for about 2.5 hours, after which time there is a gradual clearance, so that less than 10 per cent of the maximum radioactivity remains after about 10 hours. The uptake of the 99m-Tc by other organs such as the liver, spleen, pancreas, kidney, and brain reaches a maximum at about one hour, at which time the activity in all organs is less than 10 per cent of that seen in the salivary gland on a per gram basis. These data together with 99m-Tc clearance measurements in patients indicate that the radiation exposure to patients is quite low despite the use of 10 millicuries for an adult patient (Table 1).

The value of conventional scanning in the diagnosis of disease in various body organs is well established.[5] The scintillation camera, on the other hand, is a new instrument designed for comparable studies but not yet fully evaluated. This unit has no moving parts as does a scanner and functions in a manner quite analogous to an x-ray fluoroscope. Thus the entire field of view (11 inches in diameter) is presented to the read-out device (Cathode ray tube) which is viewed by a polaroid camera. A variety of control settings have been tried with the scintillation camera. It is found that a window setting of 20 (0.2 of the widest window obtainable) appears to give optimal results (i.e., the best counting rate with a minimal loss in resolution). This represents a window which is approximately 20 per cent of the gamma photon energy being analyzed. A count-rate meter facilitates voltage adjustments for optimal count rate for the selected window setting. The optimum threshold setting for this device appears to be 5.5 volts. With our scanner, conventional technique has been used for 197-Hg. scans, whereas maximum speed obtainable (60 cm. per minute) has been used for all 99m-Tc scans.[4]

The 11-inch diameter crystal of the scintillation camera is adequate in size for most studies. There are situations (visualization of lungs or hepatomegaly) in which a larger field of view would be desirable. The collimating system appears to be the factor which limits the resolution obtainable with our model of the scintillation camera. This is most apparent for the lower energy gamma emitters. A thinner lead collimator than is currently available with a greater number of holes and thinner septa would probably improve sensitivity and also permit better resolution for use with radioisotopes such as 197-Hg.

Results

Phantom studies performed with 99m technetium with both camera and scanner indicate that comparable resolution is obtainable with either unit if there is adequate control of technical factors. "Tumors" of various sizes, concentrations, and locations have been studied. It is found that approximately 200,000 total counts should be accepted in the scintillation camera to obtain about comparable resolution using our technique for scanning (four scanning lines per centimeter) using a Picker Magnascanner

TABLE 1
Radiation Dosage for Brain-scanning Agents

Isotope	Amount Used	Total Body Dose (Rad)	Target Organ (s) Dose (Rad)	
99m-Tc	10mCi	0.1-0.2	0.5-1.0	Stomach & Salivary Glands
			1.0-1.5	Thyroid
			1.5-2.5	Large Bowel
197-Hg.	10μCi/Kg.	0.02	3-12	Kidney
203-Hg.	10μCi/Kg.	0.18	30-120	Kidney
I^{131}HSA	5μCi/Kg.	0.4	0.4	Blood, Thyroid

with a 3-inch diameter crystal. It is possible to demonstrate laterally placed "tumors" of 2.5, 5.0, and 10.0 cc. volume provided the radioactive concentration is at least seven, four and two times greater, respectively, than the concentration of surrounding brain-tissue equivalent material. Pseudo-tumors placed more medially in the phantom require relatively greater concentration differences for visualization. Comparable studies performed with our camera and scanner using 197-Hg. in the phantom have yielded similar results. It is our impression that slightly better "tumor" delineation is possible with 99m-Tc, particularly for those located near the mid-line, although further study of the factors used with these instruments is necessary to prove this point.

For brain studies we normally obtain four views of the head; because of the camera maneuverability we are able to do these studies in one of several patient positions. The position is usually selected on the basis of the comfort of the patient. For studies with 99m-Tc we give six to 10 millicuries intravenously. In our experience, the optimum time for camera pictures and scans appears to be about two hours after administration of the isotope. The count rates obtained with the camera vary from 150,000 to 350,000 cpm using 99m-Tc. We feel that at least 200,000 total counts and preferably 500,000 should be obtained for the best results. For studies using radioactive 197-Hg. chlormerodrin, we use one millicurie of isotope for the average adult patient. This is administered intravenously and the camera pictures and scans made three to four hours later. We find that 100,000 total counts per projection are usually sufficient for a good camera study with 197-Hg. More total counts would be desirable, but count rates of about 15,000 cpm limit the time available per projection.

TABLE 2
Comparison of Scanner and Camera for Evaluation of Brain Pathology

(A) 99m-Tc — (6 to 10 millicuries per patient)

Scanner	Camera	No. Patients
+	+	22
+	±	2
±	+	3
±	±	8
—	—	68
		103

(B) 197-Hg. Chlormerodrin (0.6 to 1.0 millicuries per patient)

Scanner	Camera	No. Patients
+	+	28
+	±	3
±	+	2
±	±	9
—	—	68
		110

TABLE 3
Comparison of 99m-Tc and 197-Hg. for Evaluation of Brain Pathology (18 Patients)*

99m-Tc	197-Hg.	No. Patients
+	+	5
—	—	10
±	±	2
±	—	2
—	±	0
+	—	1
		20

*Studied with both scanner and camera

More than 200 brain studies have been performed to date using the scintillation camera. The majority of these patients were also scanned with our Picker Magnascanner for purposes of comparison. To date we have found that almost all brain lesions visualized using one of these units may also be demonstrated by the other. In one study of a patient with a brain abscess, the lesion was visualized more clearly on the camera picture than it was on the scan. Results of our patient studies are shown in Tables 2 and 3.

Included are reproductions of scintillation camera pictures and conventional scans on two of our patients. 197-Hg. chlormerodrin was used in one patient study and 99m-Tc in the other.

Case 1

This three-year-old boy was seen by a private physician when his parents noticed proptosis of the left eye and increasing irritability. Signs of increased intracranial pressure were found during physical examination. Surgery was performed in October, 1963, with discovery and incomplete removal of a left optic glioma invading the frontal lobe. The patient did well postoperatively until March, 1965, when increased irritability and increased intracranial pressure were again noted. A brain study was done following intravenous administration of 200 microcuries of 197-Hg. The accompanying photographs (Figure 1) demonstrate the lesion that was seen with the scintillation camera and a conventional scan. Surgery was performed and a large recurrent tumor was found in the area shown.

Case 2

This 26-year-old male was seen in July, 1964, complaining of persistent headache and increasing lethargy. A brain scan was performed using 600 microcuries of 197-Hg. and showed increased activity in the left parietal area. Angiography also indicated a space-occupying lesion in the same position. At surgery a grade III astrocytoma of the left parietal lobe was removed. This patient did well until April, 1965, when headaches recurred along with bulging of the bone flap in the area of the initial surgery. A study performed at that time with 99m-Tc and the scintillation camera showed recurrence of the tumor (Figure 2).

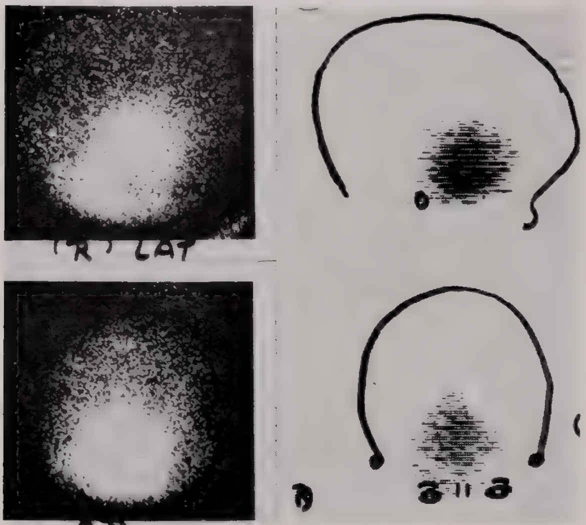

Fig. 1 — Anterior posterior and right lateral skull projections of a 3-year-old boy with recurrent optic glioma. The pictures on the left were taken with the scintillation camera and those on the right were done using the conventional magnascanner. 197-Hg. chlormerodrin was used for this study.

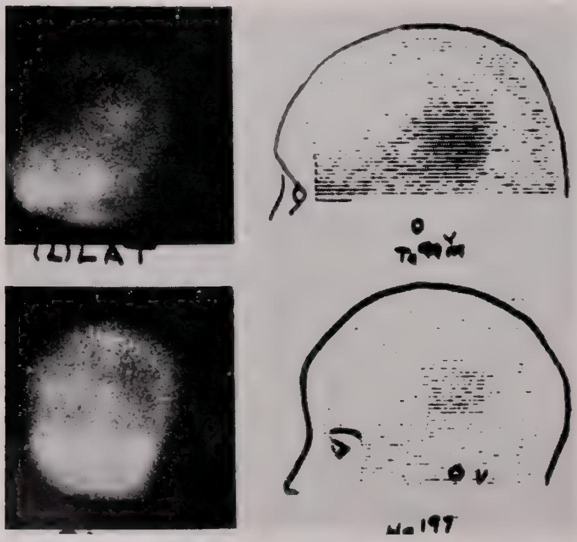

Fig. 2 — Posterior anterior and left lateral skull projections of a 26-year-old man with a left parietal lobe astrocytoma. The two pictures on the left were obtained with the scintillation camera of the PA (lower left) and left lateral positions (upper left). The two scans on the right were left lateral projections of the same patient using 99m-Tc (upper right) and 197-Hg. (lower right).

Discussion

A conventional scanner and a scintillation camera are being used to evaluate brain pathology in patients who have received either 99m-Tc pertechnetate or 197-Hg. chlormerodrin by intravenous route. The scintillation camera is a relatively new device and 99m-Tc is a recent addition to our armamentarium of radioisotopes. Thus evaluation of techniques and radioisotopic agents has been undertaken.

By virtue of its design the scintillation camera is of greatest potential value when used to study organs containing a relatively large amount of radioactivity. This combination permits data to be accumulated in a short period of time so that multiple projections of the organ and/or time-lapse studies of the clearance of radioactivity from the organ may be undertaken.

The use of large amounts of radioactive materials in patients is frequently contraindicated because of radiation hazards involved. This problem may be eliminated, at least in part, by using very short-lived radioactive materials such as 99m-Tc (Table 1). Its short physical half-life of six hours and its emission of a single gamma photon of 140 Kev. gives it nearly ideal physical properties for use with the scintillation camera. It is also being used with conventional scanners, but to some degree its value is compromised because of the finite speed obtainable with the scanning units.

Results of phantom studies indicate that foci of 99m-Tc or 197-Hg. in pseudotumors may be demonstrated as readily with the scintillation camera as with a scanner. Likewise brain pathologies (primary neoplasms, metastases, subdural hematomas and brain infarction) appear as well visualized with 99m-Tc pertechnetate as with 197-Hg. chlormerodrin which has been the principle agent for brain-tumor diagnosis for the past several years (Tables 2 and 3).

We are depending more and more upon 99m-Tc and the scintillation camera for study of patients suspected of having brain pathology. Advantages of the camera include the shorter time per projection (two to four minutes as compared with 15 to 30 minutes for a conventional scan) and the ease of positioning the camera for various patient views. Thus patients may assume reasonably comfortable positions during studies and are not required to remain immobile for nearly as long periods of time as are required for scans. Furthermore, more patients may then be studied during the working day, which is an important factor for a busy clinic.

We have found that the small polaroid picture obtained with the scintillation camera is somewhat more difficult for us to interpret than is the life size scan. This is partially due to our limited experience with the camera as compared to a much greater experience with conventional scanning. By making slides of the camera pictures and projecting these on a screen, we find that interpretations are easier to make.

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IT'S THE LAW

Doctor's Opinion Based on Misinformation Shall Be Disregarded

An orthopedic surgeon's opinion that the back condition of a claimant for workmen's compensation benefits could conceivably have been caused by an injury received in an industrial accident must be disregarded, since it was based on an incorrect medical history given him by the claimant, a Louisiana intermediate appellate court ruled.

The claimant was injured when a grinding stone he was using broke apart and part of it struck him in the abdomen. He was treated by his employer's doctor.

Fifteen months later, the claimant consulted the orthopedic surgeon because he was suffering from low back pain. The claimant told him that X-rays were taken, at the time of the accident, in a position similar to that used by the orthopedic surgeon in X-raying his lower back and told him that he had been given crutches the next day. The orthopedic surgeon concluded from that information that the claimant's present disabling back condition could conceivably have been caused by the accident.

The employer's doctor testified that no X-rays were taken of the claimant in connection with the treatment of his injury. The crutches were given to him merely because he complained of back pain which the doctor could not relate to the claimant's injury.

Since the orthopedic surgeon's conclusion was based on incorrect factual premises, it must be disregarded; and it could not be said that the accident even "conceivably" could have caused the claimant's present back condition.

Gilmore v. Brown and Root Company, 160 So.2d 836 (La., Feb. 3, 1964; rehearing denied, March 2, 1964)

Work

I do most of my work sitting down; that's where I shine. — Robert Benchley

Primary Lymphosarcoma*

PAPAIOANNOU[1] SUMMARIZED primary lymphomas of the lung recording a total of 93 cases. Seventy-seven of these were classified as a type of lymphosarcoma, 16 as reticulum cell sarcomas. There was no localized Hodgkin's disease of the lung. Thirty per cent of the 93 patients had asymptomatic nodules discovered on routine chest x-ray. Interestingly, the five-year survival for localized lesions of the lung was 45%.

An example of a patient with such a primary lymphosarcoma is presented.

Case Report

A forty-one-year-old white male was seen on a routine physical examination November 4, 1964. The patient entered the doctor's office for an annual physical examination as well as for investigation of a mass in the right submaxillary area, which had recently become noticeable but was asymptomatic. He had no other symptoms by history and system review.

The general physical examination was noncontributory except that there was a firm nontender mass in the submaxillary gland area on the right and one lymph node palpable in the right cervical area. Other lymph nodes were not enlarged. The chest, heart, abdomen, etc., were essentially normal. An electrocardiogram was also normal. The hemoglobin was 14.8 grams, the white blood cell count 11, 140; the differential cell count was 65% neutrophils and 35% lymphocytes; the sedimentation rate was 5 mm. per hour. The patient was wearing contact lenses because of bilateral cataract surgery in 1960 and 1961.

A routine chest x-ray was taken and demonstrated a coin lesion appearing as a round circumscribed mass in the right lower lung field. The chest x-rays of 1957 and 1961 were then reviewed. The lesion was definitely present, although 50% smaller in 1961. In the chest x-ray of 1957 the lesion was identified by "retrospective localization." The heart and lungs were otherwise normal.

Bronchoscopy and a right bronchogram were performed on January 15, 1965, and were interpreted

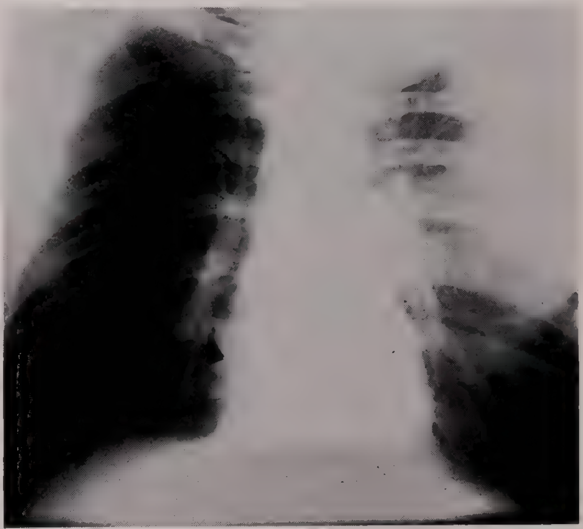

Fig. 1 — The standard chest roentgenogram demonstrates the round lesion (arrows) adjacent to the right inferior mediastinum. (November 4, 1964).

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An Interesting Solitary Lesion of the Lung

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as normal. The mass was at the bifurcation of the middle and lower lobes. Repeated sputum cytology studies demonstrated no evidence of malignant cells, and laminography demonstrated no calcium in the lesion.

An exploratory thoracotomy was performed on January 19, 1965, at which time a 3-cm. round, firm, brownish-red lesion was removed from the area of the bifurcation of the pulmonary artery into the lower and middle lobes. This lesion was directly adjacent to the bronchus and lay in the oblique fissure. Near it were several lymph nodes that were "normal" on histological study. In the region of the bifurcation of the trachea was a large mass of lymph nodes extending onto the left main stem bronchus as well as into the right main stem bronchus. The lymph nodes and the rounded lesion in the hilar area demonstrated the same histological pattern. The patient's postoperative course was essentially uncomplicated.

On January 25, 1965, the right submandibular lesion was removed as well as one other lymph node in the neck.

The pathological interpretation of the masses in the neck, the mediastinum and lung was "malignant lymphoblastoma of the nodular type (lymphosarcoma)." The patient received cobalt irradiation.

It is interesting to speculate that this man's primary lesion of the lung had been present since 1957, and was definitely discernible in 1961. In the absence of other localized areas of disease from the patient's numerous physical examinations, it would seem unquestionable that the primary lung lesion remained as such during these years. The eruption of similar lesions in the cervical area and in the mediastinum is puzzling. Such lesions might represent metastases from the original lesion in the lung but

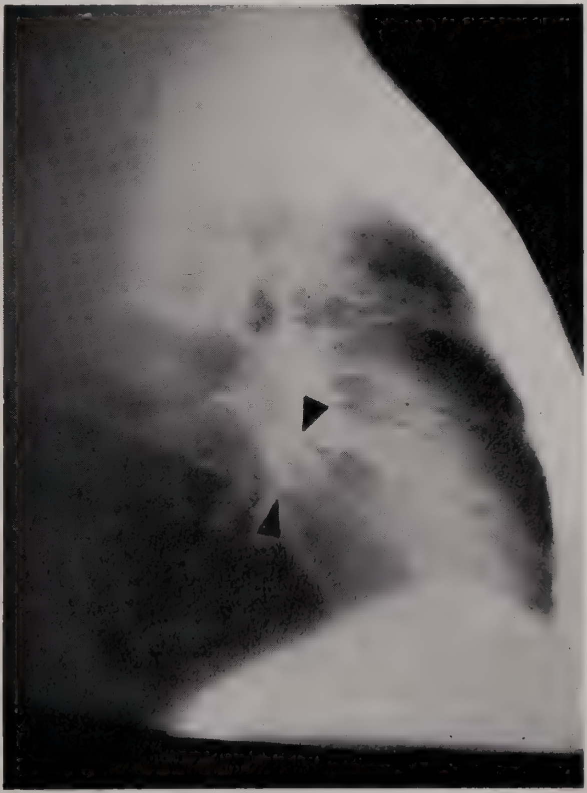

Fig. 2 — The right lateral chest roentgenogram illustrates nicely the relationship of the coin lesion to the division of the right middle and lower lobe bronchi. (November 4, 1964).

could actually be other primary foci that have arisen. The adjacent lymph nodes near the primary lesion in the lung were not involved by neoplasm. Likewise, the submaxillary area is not the usual drainage site for lesions within the lung.

Summary

An interesting case is presented of a 41-year-old white male with primary lymphosarcoma of the lung presenting as a coin lesion and with a known duration of three years.

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CUSHING'S SYNDROME

Cushing has described three separate syndromes.

Cushing syndrome No. I is a multiglandular disorder ascribed to a basophilic adenoma of the pituitary. This may be recognized shortly after birth, but is most commonly observed in females during the child-bearing age.

The symptoms consist of fatigue, weakness, weight gain, nervousness, irritability, depression, and amenorrhea or menstrual irregularity. There is associated hirsutism with male distribution of pubic hair, thinning of the skin and well marked purplish abdominal striae. Acne may be present. The broad, moon-shaped face and obesity are largely confined to the head, neck and trunk and there may be a characteristic "buffalo hump" with hypertrophy of the clitorus, arterial hypertension, osteoporosis of the spine and pelvis, polycythemia, lymphopenia and mild insulin-resistant diabetes. There is a marked increase in the urinary output of 11-oxysteroids and a moderate increase in the 17-ketosteroid excretion. Most authorities now agree that the primary factor in this syndrome is an overactivity of adrenal cortex in which hyperadrenocorticism is bilateral in 60 per cent of the cases. The exact relationship of the consistent basophilic changes in the anterior pituitary to the adrenal overactivity is not known.

Cushing's syndrome No. 2 (Meniere's syndrome) is manifest by tinnitis, deafness, disturbances or loss of labyrinthine functions, hyperesthesia of the face, diminished corneal reflex and paresis of the facial and external rectus muscle. It is caused by involvement of the fifth, sixth, seventh and eighth cranial nerves, most commonly a tumor.

Cushing's syndrome No. 3 (Chiasmal syndrome). In this syndrome, there is bitemporal hemianopsia and gradual progressive failure of vision.

This is frequently the result of suprasellar meningioma or a primary intrasellar tumor. The prognosis of this condition depends upon the type of lesion and its accessibility for surgical removal.

Durham, Robert H. — Encyclopedia of Medical Syndromes.
Hoeber Medical Division,
Harper and Row, New York

Drive Safely

There are too many people in too many cars in too much of a hurry going in too many directions to nowhere for nothing. — Coastal

Vein Stripping in Pregnancy*

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In 1952 a series on vein stripping in pregnancy was reported by the above authors.[1] This work has been continued to the present time, with few changes since the original report. The current paper is a long-term follow-up study of the procedure and an evaluation of its present status.

During 1945 to 1950 a few early reports on vein stripping were being published in this country.[2-4,6,7] This old procedure was being revived because 25 years of experience with the saphenofemoral ligation had proved disappointing. At the present time vein stripping has become the accepted method of surgical treatment for incompetent veins. While this procedure offers no assurance of good results, it is the most satisfactory form of treatment available, provided it is properly done and the basic altered physiopathology is well understood.[5]

In 1948, after vein stripping had become routine treatment for incompetent veins, a few cases of severe varicose veins in pregnancy were referred to one of us (F. W. Q.) for treatment. Should these women, in marked distress from their varicosities, be given only bandages, injections, saphenofemoral ligation; or should they be given the identical treatment of the nonpregnant patients, i.e., routine radical vein stripping?

We elected to perform routine vein stripping. Rigid criteria for operation were adopted and have been followed for the past 15 years. These patients have been periodically surveyed, and the series has grown to 134 cases. Ninety patients of this group have been recently surveyed. The results, complications, and subsequent pregnancies of this group constitute this report.

Indications for Surgery in the Pregnant Patient with Varicose Veins

Before accepting a pregnant patient for vein surgery, we had to be assured that the patient had had incompetent veins in the nonpregnant state. A history of phlebitis in the pregnant patient with varicose veins and the severe sequelae associated with this complication constituted an additional indication for surgery.[8,9,10] The fourth to the seventh month of gestation was considered the most appropriate period, for by this time the signs and symptoms of varicose veins were advanced. Furthermore, the risk of fetal exposure to drugs, toxins, environmental changes, as well as incidence of spontaneous abortion, are greatest during the first trimester. Therefore surgery was delayed in every instance until the fourth month, and rarely performed after the seventh month.

Vein Stripping in General

For a better understanding of this disorder, a few basic facts should be explained to the patient before he undergoes surgery:

1. Varicose veins are a constitutional weakness, and therefore cannot be cured but only improved. Pregnancy is only one of several aggravating factors.

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*Presented April, 1965 at the Minnesota Obstetrical and Gynecological Society Meeting in Duluth, Minnesota.

2. "Recurrences" (which are actually enlarging pre-existing veins rather than recurrences as such) are inevitable and follow-up care is essential. This is a life-long problem.

3. Although incompetent veins may be asymptomatic, they are nevertheless best treated by eradication in order to avoid the numerous potential complications which may ensue.

4. Symptoms are due to a hemodynamic disorder,[11] which medicine will not improve; elastic supports are temporizing, and injections are unsatisfactory except in the minor varices or branches. Eradication by radical stripping is the most satisfactory form of treatment.

Technical Considerations

The most important factor in obtaining good results in vein surgery is quantitative excision. Meticulous care in removing all incompetent veins, particularly the incompetent perforators, is most important.

Vein surgery should not be the time-consuming, laborious operation often depicted. By utilizing a planned, efficient procedure one can perform the average operation in less than one hour per leg.

In general, the surgical technique and postoperative care (Figure 1) are the same for the pregnant and the nonpregnant group. Pentothal anesthesia and intratracheal intubation and high O_2 flow are given to all patients. Complete eradication of the incompetent veins in the pregnant group requires a bit more time and diligence. The postoperative injection period is likewise more prolonged and tedious in the pregnant group. One finds, however, that after delivery, with consequent decreased venous pressure, the final results are excellent. In other words, the operator is less likely to overlook the small incompetent varix or perforator in the pregnant patient.

Postop.

1. Anticoagulants — If Indicated
2. Pressure Dressing — 6 Yd. Roll & Ace Bandages
3. Tub Bath with Dreft after 24 Hours
4. Thereafter Ace Bandages as the Only Dressings
5. Walk Ad Lib
6. Above Knee Supports 2 Wks.
   Below Knee Supports 4 Wks.
7. Injections If Needed
8. Return Every 6 Mos.

Fig. 1 — Postoperative vein stripping routine.

All of the nonpregnant patients should be given preoperative anticoagulants if there is a history of thromboembolic phenomena. Therapy should be continued postoperatively for varying periods of time.

Today, vein surgery is offered early as a prophylactic measure, whereas in the past, surgery was delayed until symptoms were severe.

Results

Previous thrombophlebitis with damaged deep veins will influence the results. Both the pre and postoperative evaluation will vary with the time of day depending upon the patient's activity.

As seen by Table 2, the final results of the pregnancy group collected over a 15-year period differ little from those of a group of nonpregnant patients reviewed consecutively in a period including 1957-58.

Of further interest in the pregnancy group is the incidence of full term pregnancies (Table 2). Of those coming to surgery, there was an average parity of 4.3 with an average

Vein Stripping

Patients	Subsequent Surgery	Pregnancies	Factors in Recurrence
152 Routine 1957-'58	14 %	———	Pregnancies Thrombophlebitis Follow-Up Failure
90 Pregnant 1948-'63	16.1%	Before Surgery 4.3 After Surgery 1.2	Pregnancies Thrombophlebitis (11%) Follow-Up Failure (22%)

Fig. 2 — Long-term comparative follow-up between routine vein stripping and vein stripping performed during pregnancy.

of 1.2 subsequent pregnancies after surgery. Indeed, of the 90 patients operated, 12 had three or more babies after surgery. Two thirds of the group had one or more babies after surgery.

Comments

This extended follow-up on this group of operated pregnant patients would seem to indicate that the results are comparable with those in the nonpregnant group. Their pregnancies were made more comfortable, and they were also less susceptible to complications of varicose veins during pregnancy by having had the immediate active treatment.

It would seem that it is not the best and most humane medical judgment to advise a young woman to defer vein surgery until her child bearing is over.

Sufficient time has elapsed to allow an adequate study of the children who were en utero during vein surgery. There was one intrauterine death which occurred a few days before term, etiology of which was indeterminate. This was three months following surgery. There are two children with mental retardation, one of whom is able to attend public school. The second child attends a special school and, in addition, has a congenital wrist drop. Two congenital defects among 89 live births is well within the expected range as outlined by the National Foundation.[12] Three and five-tenths per cent of live births have recognizable congenital defects. At the end of one year the incidence is raised to six and nine-tenths per cent.

Summary

A long-term survey of a group of patients undergoing vein surgery during pregnancy is presented. Their management and final results are compared with a series of nonpregnant patients having similar surgery performed by the same operator.

It is apparent that only a small percentage of pregnant patients have severe varicose veins and are candidates for surgery during their pregnancy. Careful selection of such patients is extremely important. When surgery is indicated, the patients can be made much more comfortable for the remainder of their pregnancy. The final results are satisfactory and compare favorably with those of the nonpregnant group. There appears to be no risk to mother or child if this procedure is carried out after the first trimester.

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The Superior Man — Confucius (551 to 479 B.C.)

The superior man hates those who like to criticize people or revel in their weaknesses. He hates those who in the position of inferiors like to malign or spread rumors about those in authority. He hates those who are chivalrous and headstrong but are not restrained by propriety. He hates those who are sure of themselves and are narrowminded.

Idiopathic Hypertrophic

IDIOPATHIC HYPERTROPHIC subaortic stenosis, also known as muscular subaortic stenosis, is a condition in which there is an obstruction at the outflow tract of the left ventricle because of hypertrophy of the interventricular septum and free wall of the left ventricle. Although cases were reported prior to 1957, the entity has received increased investigation since that date. The following summaries of the clinical examination and cardiac catheterization data of three patients point out the pertinent features of this syndrome.

Case Reports

Case 1.

A 33-year-old male was discharged from the United States Navy in 1953 with a diagnosis of ventricular septal defect. This had not been verified by cardiac catheterization. He first noted anginal chest pain and dyspnea on exertion in 1956. Cardiomegaly was noted in 1964 (Figure 1); at this time a harsh grade iii/vi systolic murmur was heard at the left sternal border with radiation to the axilla and the neck.

The point of maximum impulse was in the fifth intercostal space midway between the anterior axillary line and the midclavicular line. The aortic second sound was present and was louder than the pulmonic second sound. Cardiac cinefluoroscopy demonstrated left ventricular enlargement and absence of intracardiac calcification. The electrocardiogram was interpreted as revealing left ventricular hypertrophy (Figure 2). A diagnosis of aortic stenosis was made and a thoracotomy performed in 1957. At operation the aortic valve was found to be normal.

The patient had a stormy postoperative course characterized by infection of the chest wall and the development of prominent Q waves in leads II, III and AVF. Since 1957 left-heart catheterization has been performed on three occasions and has shown left ventricular-subaortic peak systolic gradients of 30, 52 and 88 mm. Hg. respectively. Right-heart catheterization revealed a peak systolic gradient of 10 mm. Hg. between the right ventricle and

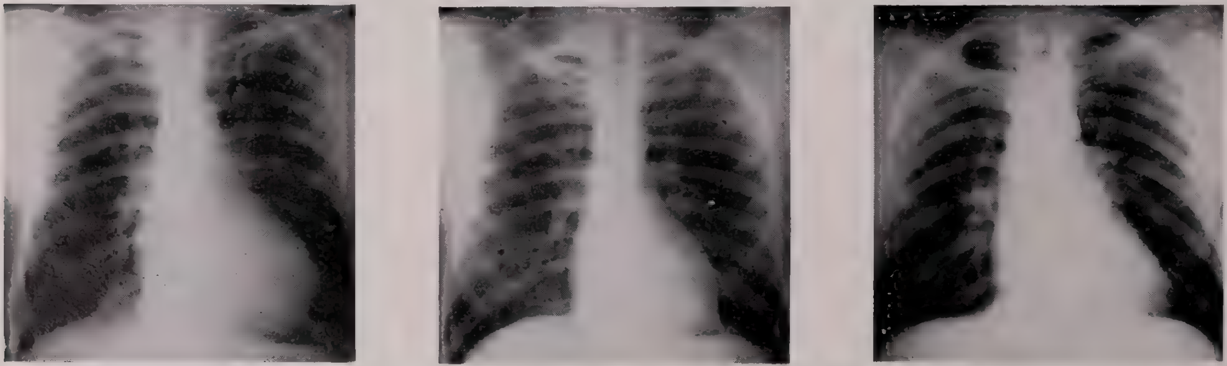

Fig. 1 — *Left.* Case 1. P-A chest x-ray taken in 1964. *Middle.* Case 2. P-A chest x-ray taken on admission. *Right.* Case 3. P-A chest x-ray taken on admission.

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**See Test Your Word Score Page 271.

Subaortic Stenosis

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infundibular area of the right ventricle. A left ventricular angiogram demonstrated an S-shaped left ventricular cavity formed by the hypertrophied interventricular septum. Marked thickening of the free left ventricular wall was also present (Figure 3).

Case 2.

A 39-year-old male presented with a two-year history of exertional dyspnea, angina occurring at rest, and dizziness. A heart murmur had first been noticed eight years prior to the development of symptoms. Physical examination revealed a grade iii/vi systolic murmur at the left sternal border with radiation into the neck. The aortic second sound was normal. Radiologically, left ventricular prominence was noted (Figure 1), and on cinefluoroscopy, intracardiac calcification was absent. The electrocardiogram was interpreted as left ventricular strain (Figure 2), and the vectorcardiogram as left ventricular hypertrophy (Figure 4). Left heart catheterization was performed. There was no systolic pressure gradient between the aorta and left ventricle at rest, but following an Isuprel infusion a peak systolic gradient of 68 mm. Hg. was obtained (Figure 5). A peak systolic gradient of 128 mm. Hg. was noted following a premature ventricular contraction (Figure 5). Brachial artery and left ventricular pressure curves had peak systolic velocities which were increased in contrast to the pressure curves of aortic valvular stenosis, in which the first derivative of the brachial artery pressure curve is reduced.[1] Pulsus bisferiens** was present. A left ventriculogram revealed an outflow obstruction during systole. The aortic value appeared normal (Figure 6).

Case 3.

A 44-year-old male presented with a two-year history of exertional angina, dyspnea and dizziness, usually relieved by resting for a 20-minute period. The chest x-ray revealed left ventricular prominence (Figure 1). A grade iv/vi, harsh, medium-pitched systolic ejection murmur with radiation both to the neck and to the axilla was heard at the fourth intercostal space at the left sternal border. The aortic second sound was present. The electrocardiogram was consistent with ventricular hypertrophy (Figure 2) as was the vectorcardiogram (Figure 4). Left heart catheterization revealed a peak systolic gradient of 25 mm. Hg. at rest (Figure 7). A prominent atrial contraction was also noted. A left ventricular injection showed narrowing of the left ventricular cavity with marked hypertrophy of the left ventricular wall. The aortic valve appeared normal (Figure 6).

Discussion

This syndrome occurs in young adults of

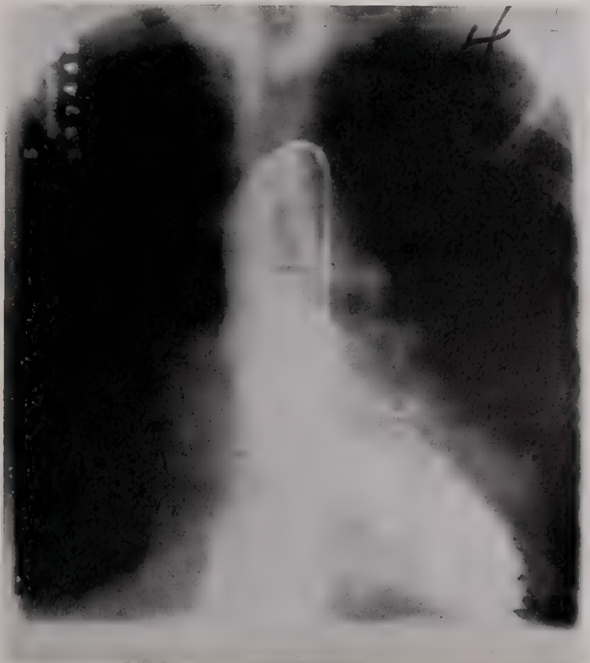
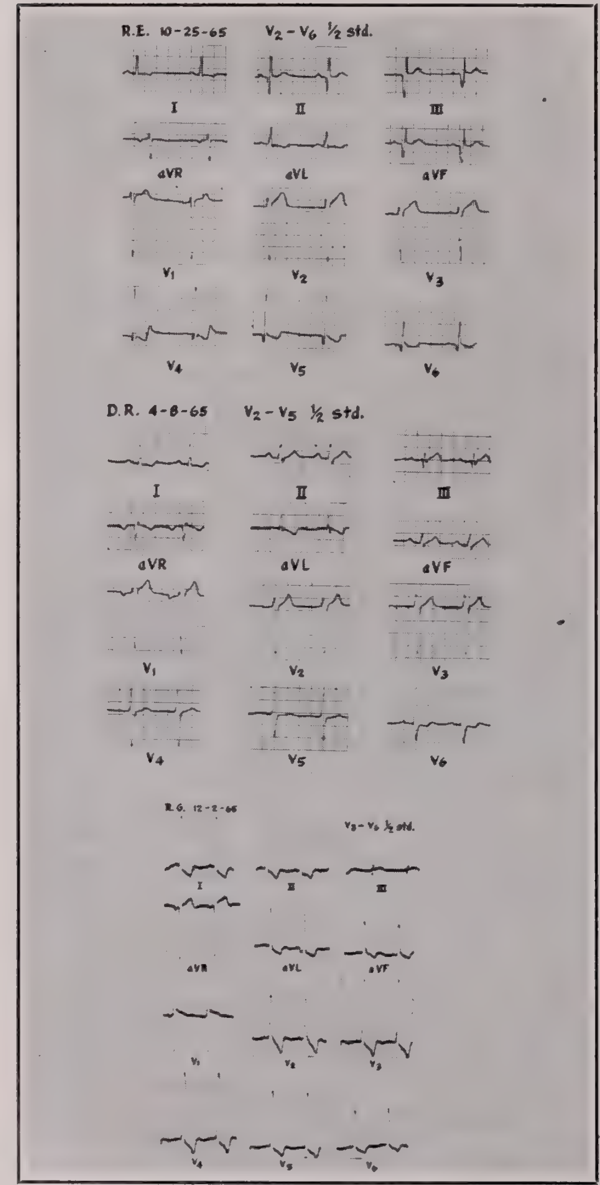


Fig. 3 — Contrast media has been injected into the left ventricle. There is increased thickness of the myocardium between the ventricular cavity and the lateral heart border. An area of narrowing in the left ventricular outflow tract is present overlying the spine.

either sex, although males predominate. Some of the cases have been familial.[2] Symptoms are generally progressive, usually consisting of dyspnea on exertion, anginal-like pains which are often atypical in nature, dizziness and syncope. A rare but characteristic symptom is the presence of dizziness or syncope following an episode of sneezing or paroxysmal coughing. The symptoms are thought to result from a hypertrophied, poorly distensible left ventricle with low muscular compliance. The lack of ventricular compliance presents an increased resistance to diastolic filling, raises the left atrial pressure and sets the stage for dyspnea. The left ventricular end-diastolic blood volume is low, resulting in a low stroke volume and a reduced cardiac output. A harsh, loud, medium-pitched systolic murmur, heard best at the left sternal border or apex, is always present and may radiate to the base or axilla. This murmur may be confused with aortic stenosis, interventricular septal defect or mitral insufficiency. In fact, mitral insufficiency is often concomitantly present. A mild amount


R.E. 10-25-65
V₂ - V₆ ½ std.
I
II
III
aVR
aVL
aVF
V₁
V₂
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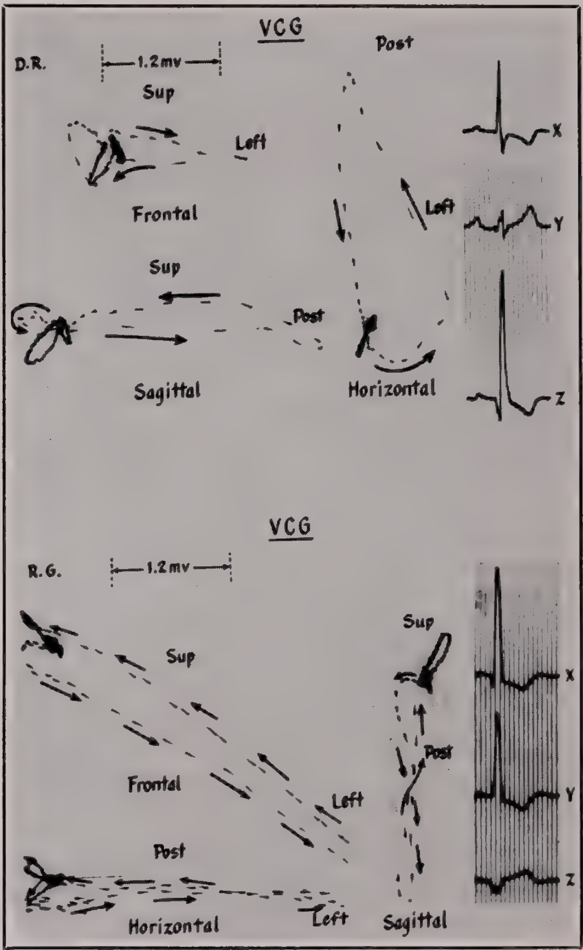
V₄
V₅
V₆
D.R. 4-8-65
V₂ - V₅ ½ std.
I
II
III
aVR
aVL
aVF
V₁
V₂
V₃
V₄
V₅
V₆
R.G. 12-2-66
V₃ - V₆ ½ std.
I
II
III
aVR
aVL
aVF
V₁
V₂
V₃
V₄
V₅
V₆

Fig. 2 — *Top.* Electrocardiogram of Case 1. There are significant Q waves in leads II, III, and aVF which occurred following surgery and probably represent a myocardial infarction, although they are commonly seen in this condition and usually represent septal hypertrophy (see discussion). *Middle.* Electrocardiogram of Case 2. *Bottom.* Electrocardiogram of Case 3.


VCG
D.R.
1.2mv
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1.2mv
Sup
Sup
Post
Frontal
Left
Post
Horizontal
Left
Sagittal
X
Y
Z

Fig. 4 — *Top.* Vectorcardiogram of Case 2. Initial forces are normal but the voltages are increased. *Bottom.* Vectorcardiogram of Case 3. Initial forces are normal but the voltages are increased. The mean QRS vector is more inferior in contrast to Case 2 in which it is posterior.

of right ventricular infundibular stenosis may also contribute to the development of the systolic murmur. A double apical impulse, pulsus bisferiens, a paradoxically-split pulmonic second sound, and third and fourth heart sounds are often present.[3]

The electrocardiogram is usually abnormal and generally demonstrates left ventricular hypertrophy. P mitrale is frequently recorded. Prominent Q waves are common in this condition and are thought to represent septal hypertrophy and not myocardial infarction.[3]

Radiographic studies show left ventricular and often some left atrial enlargement. Calcification of heart valves and coronary arteries is typically absent. Angiography demonstrates a narrowed ventricular chamber with thickening of the interventricular septum and free wall. The shape of the left ventricular cavity is usually abnormal.[4] The bulging interventricular septum results in an inward concavity at the mid-portion of the inferior border of the left ventricular cavity (Figure 3). In addition, a "tongue-like" extension of dye is seen extending to the apex of the left ventricle in the lateral view. Filling defects of the left ventricle are frequently seen and are due to localized hypertrophy of muscle. The coronary arteries are often dilated. The most characteristic finding is the presence of a cone-shaped narrowing which lies from 2 to 4 cm. below the aortic valve. The dimensions of this narrowed area vary during different portions of the cardiac cycle (Figure 6).

Cardiac catheterization data is necessary for diagnosis. There is a systolic gradient between the left ventricular cavity and the chamber above the hypertrophied muscle and below the aortic valve. This gradient is variable and is the result of several factors: the volume of the left ventricular cavity, the force of left ventricular contraction, and the transmural pressure which distends the outflow channel during systole. These factors are influenced by the presence or absence in the patient of basal conditions, anesthesia, muscular exercise, and medications. The administration of digitalis, Isuprel or nitro-

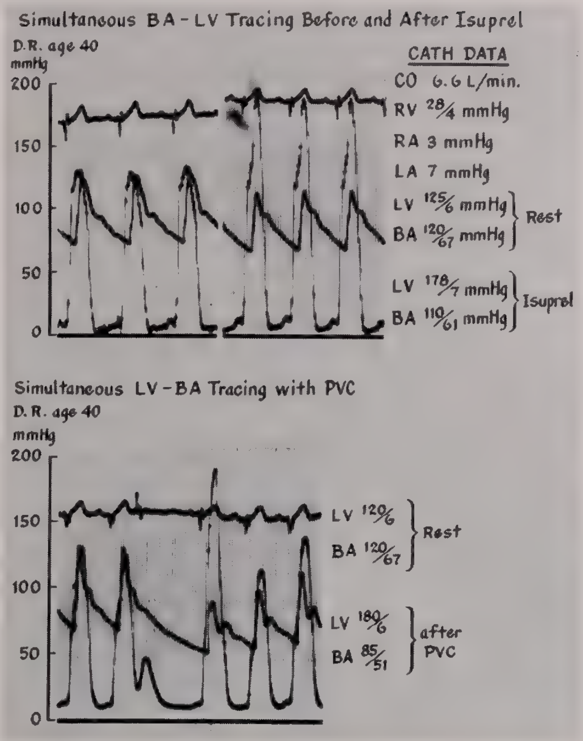

Fig. 5 — *Top.* Case 2. The electrocardiogram and the brachial artery and left ventricular pressures are recorded simultaneously before and after an isoproterenol infusion. A systolic pressure gradient of 68 mm. Hg. was obtained. Other data obtained during cardiac catheterization are listed at right. *Bottom.* Case 2. In the ventricular systole following a premature ventricular contraction, a peak gradient of 95 mm. Hg. is obtained. On another occasion a peak gradient of 126 mm. Hg. was noted. Following the premature contraction on the subsequent beat the brachial artery pulse pressure is also decreased, and several subsequent normal contractions are required before the brachial artery pressure returns to its previous level.

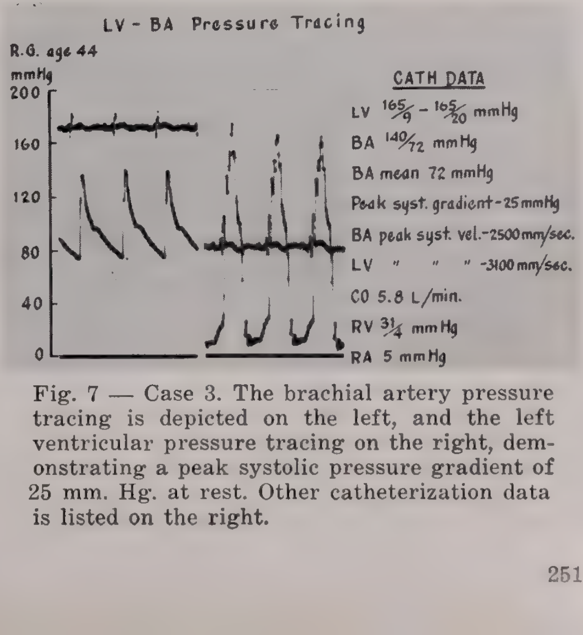

Fig. 7 — Case 3. The brachial artery pressure tracing is depicted on the left, and the left ventricular pressure tracing on the right, demonstrating a peak systolic pressure gradient of 25 mm. Hg. at rest. Other catheterization data is listed on the right.

glycerin accentuates the systolic gradient. When not present in the patient at rest, a gradient can be produced by the intravenous infusion of Isuprel,[5] or by the performance of the Valsalva maneuver.[6] This gradient is observed between the brachial artery and left ventricular pressure curves following a premature ventricular contraction[7] (Figure 5). A smaller gradient between the pulmonary artery and right ventricle is also demonstrable in some patients.

Treatment of this condition is difficult because the commonly used cardiac medications either cause no relief or tend to aggravate the symptomatology. The patient should avoid those activities which produce symptoms. Patients with more severe degrees of incapacitation have generally responded to

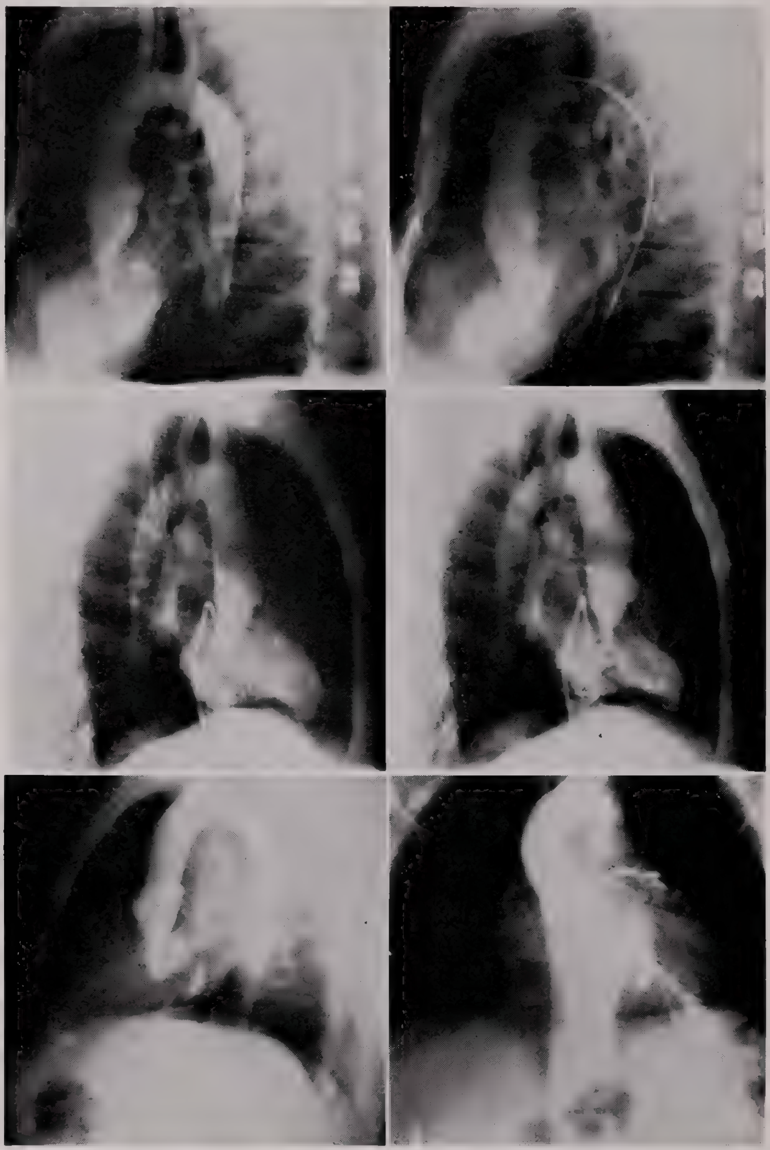

Fig. 6 — *Top.* Case 1. A cone-shaped area of stenosis can be seen approximately 4 cm. below the aortic valve. The dimensions of this stenotic area vary during different portions of the cardiac cycle *(right* and *left). Middle.* Case 2. Diastole is seen on the left, systole on the right. *Bottom.* Case 3. The stenotic area is seen as well as dilated coronary arteries. On the right is seen a "tongue-like" extension of contrast material extending toward the apex of the left ventricle. Hypertrophied myocardium almost obliterates the left ventricular cavity.

surgical removal of the hypertrophied septal tissue. Surgical mortality has been significant in the past and is the reason why more patients have not been operated. The most promising recent approach is one described by Morrow et al.[8] in which, under cardiopulmonary bypass, an aortotomy is performed and an incision made in the cardiac muscle from the stenotic area to the apex of the left ventricle, relieving the obstruction.

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WHAT'S YOUR DIAGNOSIS?

A 64-year-old female was admitted to the hospital because of crampy pain in the abdomen of a six-day duration. She had vomited on one occasion shortly after having eaten lunch with her daughter the week before. They thought the vomiting had arisen from some food dyscrasia, because both she and her daughter had vomited. The vomiting did not recur, but she then became aware of abdominal distention. There had been no previous symptoms.

The examination indicated abdominal distention, active bowel sounds suggesting intestinal obstruction, and a large pelvic mass extending into the abdomen. The mass was fluctuant in the cul-de-sac but not tender. The abdominal portion of the mass was nodular and slightly tender. The admission temperature was normal, but during the next two days the temperature fluctuated from normal to 101°. The white count was 15,900. Polymorphonuclears-77%. Hemoglobin-14 grams. Sedimentation rate-24. BUN-35. Carbon dioxide combining power-21.8. Blood chlorides 89.5. The urine revealed 1+ albumin. X-ray examination suggested the possibility of small bowel obstruction. Barium enema revealed a large extrinsic mass in the pelvis causing a narrowing at the mid-sigmoid.

Gynecological and surgical consultations were obtained. The nodular abdominal mass and the pelvic cul-de-sac fluctuation were observed by both consultants. The patient was given Thyotepa in anticipation of a contaminating operation for malignancy.

What is your diagnosis? Turn to page 256.

Power

To have what we want is riches, but to be able to do without is power.
— George MacDonald

The Doctor and Literature*

Geoffrey Chaucer

Geoffrey Chaucer, a year before his death in 1400, lost his sinecure as Clerk of the King's Works. In the *Complaint of Chaucer to His Empty Purse,* the poet humorously petitions the new king, Henry IV, for a pension, ending with the lines:

"For which unto your mercy thus
I cry
Beth heavy again or elles must I
die."

Chaucer's Doctor of Physik is characterised as a verray parfit practitioner.

Eight years of study at Oxford were required to qualify for a medical degree in the Middle Ages. The students steeped themselves in the writings of famous physicians of antiquity — Greek and Arabian — ranging from Aesculapius to Rufus.

The Doctor of Physik, when treating a patient, first cast his horoscope. It was commonly believed in Chaucer's time that every man was born under one of the twelve planets of the zodiac. One might be born under the sign of Taurus the Bull, another under the sign of Pisces the Fish.

The worthy doctor cast his patient's horoscope to determine if the concatenation of the planets were at the moment beneficent or malign. This astrological lore determined the nature of the treatment given.

Chaucer's Doctor "knew the cause of everich maladye, were it hoot or cold or moiste or drye, and where engendred and of what humour." The doctor of physic prescribed drugs to be obtained from an apothecary.

There is a touch of malice in the last line of Chaucer's Cameo. During the pestilence or Black Death, the good doctor made a fortune by prescribing gold (aurem potabile) in his philters because, being avaricious, he loved gold above all things.

The distinction between the doctor and apothecary in the Sixteenth Century was not always clean cut. An apothecary frequently prescribed and filled a prescription in one operation.

John Milton

John Milton, from 1640 to 1660, when his poetic genius was at full florescense, sacrificed twenty years, his talent and his eyesight, to write political tracts of no literary merit for the Cromwellian government of which he was Latin Undersecretary of State.

When Charles II was restored to the throne, Milton's political pamphlets were publicly burned by the common hangman and the poet had to go into hiding until a general amnesty was declared.

Lord Byron

Lord Byron died in exile, the victim of what Thomas Babington Macaulay called the English public in one of its periodical fits of morality:

"Once in six or seven years our virtue becomes dangerous. We cannot allow the laws of decency to be violated. Some unfortunate man is singled out as an expiatory sacrifice. If he has children they are taken from him. If he has a profession he is driven from it. He is cut by the higher orders and hissed by the lower. He is in truth a sort of whipping boy. At length

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*Continued from Minnesota Med 49:73, 1965.

Continued to page 280.

Intraspinal Arteriovenous Anomalies

• Surgical
• Treatment

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THE PREVIOUS treatment of arteriovenous anomalies of the spinal cord has been largely disappointing. Since January 1963, four cases have been diagnosed at the Mayo Clinic by myelography and verified by thoracic aortography. The patients were treated definitively by intrathoracic occlusion of one or more anomalous arteries from the aorta which were feeding the intraspinal lesion. Each patient presented with various degrees of paraparesis, some with and some without sensory loss.

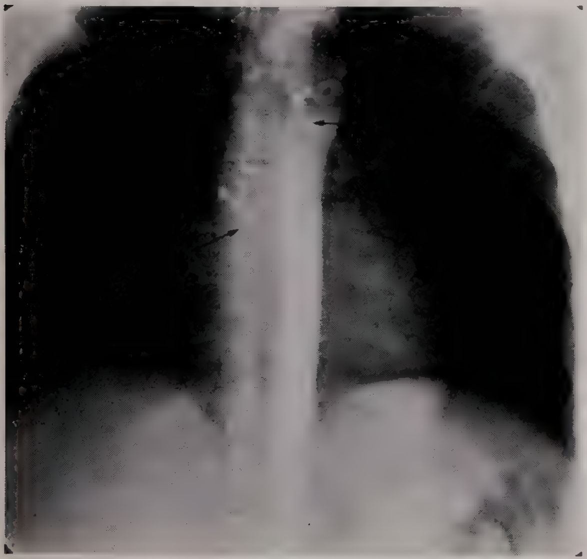

Fig. 1 — Retrograde aortogram showing two anomalous arteries: one on the left at the fourth space and another on the right at the sixth space feeding an arteriovenous lesion in the thoracic portion of the spinal cord. The opaque catheter in the aorta can be seen below.

At the time of this preliminary report the results of our surgical treatment are encouraging. What the long-term prognosis will be cannot be stated. We plan to follow these cases and to add others in a later report.

We feel that our combined efforts will help a far-from-small group of patients who, in the past, have had little to hope for and who, for the most part, have become paraplegic.

The following case illustrates the problem involved in the diagnosis and treatment of a vascular anomaly of the spinal cord.

Report of Case

A 21-year-old male college student had an insidious onset of lumbar backache which was aggravated by stress and strain. A diagnosis of lumbar muscle strain had been made and heat and analgesics had been applied. One month after backache began, while taking a shower bath, he noted that he could not feel the water over his left leg. Later he noted hyperesthesia over the right side of the chest at about the seventh and eighth dermatomes.

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We saw the patient about three months later. Myelography with Pantopaque had been carried out elsewhere. A protruded disk or neoplasm was suspected, but a diagnosis of a vascular anomaly of the spinal cord was made. The spinal fluid contained 100 mg/100 ml. of protein and the fluid was reported as being xanthochromic. In addition to the elevated concentration of protein, the fluid showed eight white blood cells and 68 red blood cells.

Physical Findings

Our examination disclosed hypalgesia at the level of the sixth and seventh intercostal spaces on the right. The loss was slightly lower and much more pronounced on the left. Loss of muscular power was not detectable, although the patient said that his left leg seemed weak. Some loss of thermal sensation was reported over the left flank. On auscultation over the spinal column, no bruit could be heard. There were no other obvious vascular abnormalities.

X-ray Studies

Roentgenologic examination of the spinal column revealed an old vertebral epiphysitis and residual opaque oil in the spinal canal. A retrograde aortogram by the Seldinger technique via the left femoral artery using 32 ml. of sodium and methylglucamine diatrizoates (Renovist) revealed two anomalous arteries from the aorta to the spinal canal and a pooling of opaque medium in large intraspinal veins in the thoracic region (Figures 1 and 2).

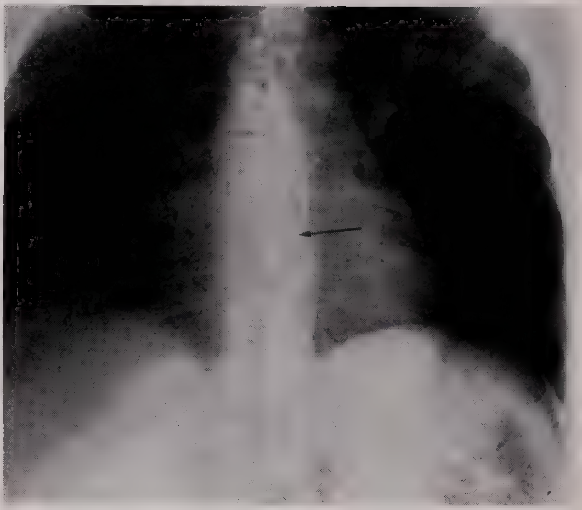

Fig. 2 — Extensive pooling of Renovist in abnormal veins in the subarachnoid space is seen (arrow) above the opaque catheter.

Thoracotomy was performed and the two anomalous arteries were occluded. The artery on the left at the fourth intercostal space was ligated and divided. The anomalous artery at the sixth space on the right was ligated but not divided.

The patient's convalescence was uneventful. The sensory deficit cleared and the feeling of weakness of the left lower extremity disappeared. He was dismissed eight days after the operation.

ANSWER TO WHAT'S YOUR DIAGNOSIS

(from page 253)

Pelvic abscess, appendical in origin; multiple myomata of the uterus. The confusing nodularity of the abdominal mass had led all of the examining physicians to the erroneous diagnosis of carcinoma of the ovary.

Have Faith

Dr. Carl Jung, famous psychiatrist, once told a sick patient that he was suffering from a lack of faith in God and immortality. The young man asked, "But, Doctor, do you believe in God and immortality?" Dr. Jung replied: "I am a doctor, not a priest. But I tell you this: If you recover your faith, you will get well; if you don't, you won't."

Church Management

We're told that there are two kinds of people in the world: the good and the bad. The good decide which is which. — Woman's Home Companion

Responsibility

It is easy to dodge our responsibilities, but we cannot dodge the consequences of dodging our responsibilities. — Animator

Bilateral Vocal-Cord Paralysis

Post Thyroidectomy Surgical Correction

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ALTHOUGH VOCAL-CORD paralysis may result from numerous causes, the most frequent cause of bilateral vocal-cord paralysis occurs from injury to the recurrent laryngeal nerves during thyroidectomy. This unfortunate surgical complication results in an inadequate laryngeal airway and a poor speaking voice. This article presents a surgical procedure which has been successfully employed by the author in twelve cases with very satisfactory results. The procedure assures an adequate airway and a useful voice.

The surgical technique was originated and explained to me by William C. Thornell, M.D., in 1952.[1] Prior to that time, like others, the author had employed various other surgical procedures which had been advocated for the surgical management of bilateral vocal-cord paralysis. These operations were successfully applied and advocated by King, Kelly, and Woodward along with other surgical modifiers. The author adopted the Thornell intralaryngeal technique because surgically it was far less complex but just as successful as the extralaryngeal approaches advocated by those before Thornell.

Bilateral Cord Paralysis

Most postoperative thyroid gland vocal-cord paralysis is unilateral and presents no serious problem, as an adequate airway exists because the opposite unaffected cord has normal excursion. The only problem resulting from a unilateral vocal-cord paralysis is hoarseness. In a bilateral vocal-cord paralysis the vocal cords are often fixed in a median line position, thereby establishing an inadequate airway (Figure 1 a, b). The patient is in an extremely critical condition and often requires an immediate tracheotomy. In some cases the median fixation of the vocal cords is not complete and a small laryngeal opening

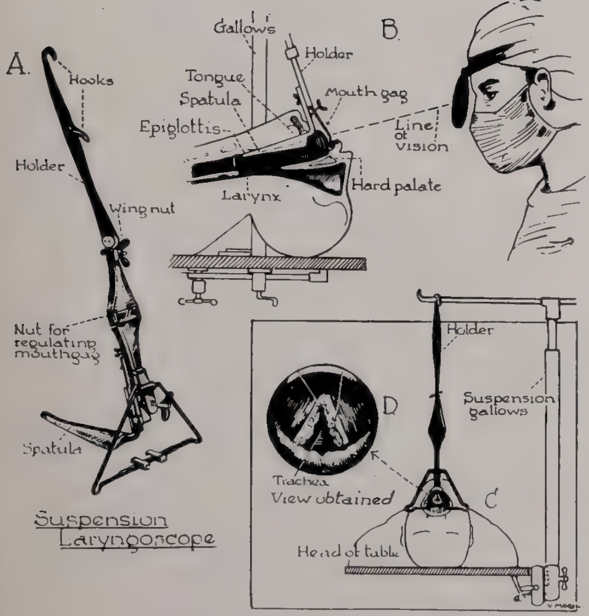
A.
Hooks
Holder
Wing nut
Nut for regulating mouthgag
Spatula
Suspension Laryngoscope
Gallows
B.
Holder
Tongue
Spatula
Mouth gag
Epiglottis
Line of vision
Hard palate
Larynx
Holder
Suspension gallows
D
Trachea
View obtained
C
Head of table

Fig. 2 — Exposure of larynx.

leaves the patient with a very restrictive airway. In such cases, any exertion results in marked dyspnea with stridorous breathing and inability to climb a flight of stairs without experiencing respiratory embarrassment. Furthermore, patients often cannot tolerate the laryngeal edema that accompanies an acute respiratory infection and will require an immediate tracheotomy in order to provide a proper airway.

It is now generally agreed that a patient who has a bilateral vocal-cord paralysis resulting in an inadequate airway which has existed for a period of at least six months should be a candidate for surgical improvement of the airway. The following descrip-

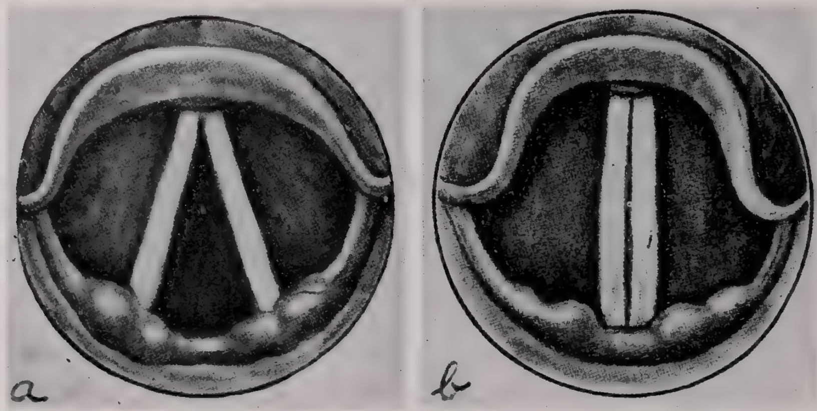

Fig. 1(a) — Position of vocal cords in normal larynx (inspiration). (b) Position of vocal cords in bilateral mid-line paralysis.

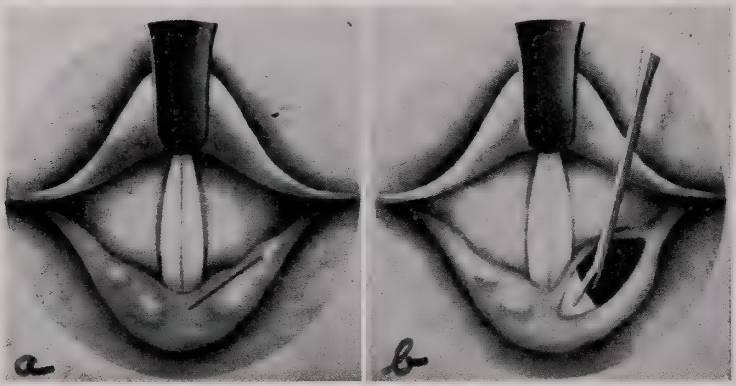

Fig. 3(a) — Incision over the arytenoid cartilage. (b) Arythenoid cartilage immobilized and denuded.

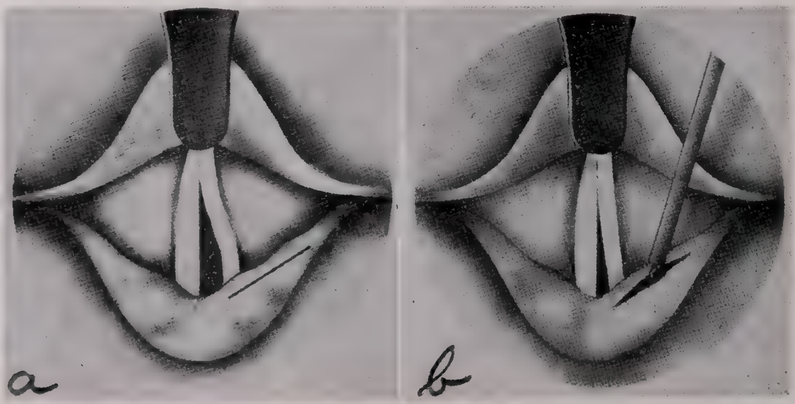

Fig. 4(a) — Position of vocal cords after right arytenoidectomy. (b) Electrocautery applied to lateral area of wound.

tion of the surgical technique of intralaryngeal arytenoidectomy* is the one which has been successfully applied by the author in twelve consecutive cases.

Surgical Procedure

Preliminary Tracheotomy

If the patient has not required a previous tracheotomy, this procedure is performed prior to the arytenoidectomy, the two procedures being scheduled together. The tracheotomy may be performed under local anesthesia, but I prefer to perform it under intralaryngeal general anesthesia and then proceed with the arytenoidectomy. In that manner, one can proceed immediately following the tracheotomy to the arytenoidectomy without interruption from the anesthesiologist and without breaking scrub technique.

Exposure of the Larynx

Following tracheotomy, the larynx is exposed by the Killian-Lynch suspension laryngoscope. A very adequate exposure of the larynx is obtained with this instrument and it affords the best visualization of the larynx by means of an operating headlight (Figure 2). After the larynx has been exposed, the operator chooses the cord upon which the arytenoidectomy is to be performed. Either cord may be selected. Being left-handed, the author has experienced more surgical ease in removing the right arytenoid and has observed that the right-handed operator is more agile in approaching the left arytenoid.

Removal of Arytenoid

Having selected the arytenoid to be removed, the corresponding aryepiglottic fold is slowly infiltrated with approximately two cc. of one per cent Xylocaine with epinephrine. As in septoplastic surgery, this infiltration serves two purposes; it minimizes the bleeding and aids in the elevation of the soft tissue from the arytenoid cartilage. Following infiltration, an incision is made over the arytenoid cartilage until its superior surface is exposed (Figure 3-a). The cartilage is grasped and immobilized, thereby enabling the operator to separate all muscle attachments from the arytenoid cartilage (Figure 3-b). This cartilage, having been denuded, is severed from its articulation with the cricoid cartilage and removed.

Results

Following disarticulation, the vocal cord promptly assumes a position lateral to the mid-line, thereby giving the desirable airway (Figure 4-a). In seven of the cases operated by the author an obturator was introduced between the vocal cords to approximate the wound edges as suggested by Thornell. The five other cases were just as effectively managed minus the obturator, providing electrocautery was applied to the lateral area of the wound (Figure 4-b). Electrocautery produces scarring and assures lateral fixation of the vocal cord. Postoperative edema is well controlled by the proteolytic enzymes, and the patient may have a liquid diet within twelve hours postoperatively.

The tracheotomy tube may be removed on the third to fifth postoperative day and the patient discharged two days afterward.

Comments

The author has experienced successful results in twelve consecutive intralaryngeal arytenoidectomies affording an adequate airway and better speech to those with bilateral vocal-cord paralysis.

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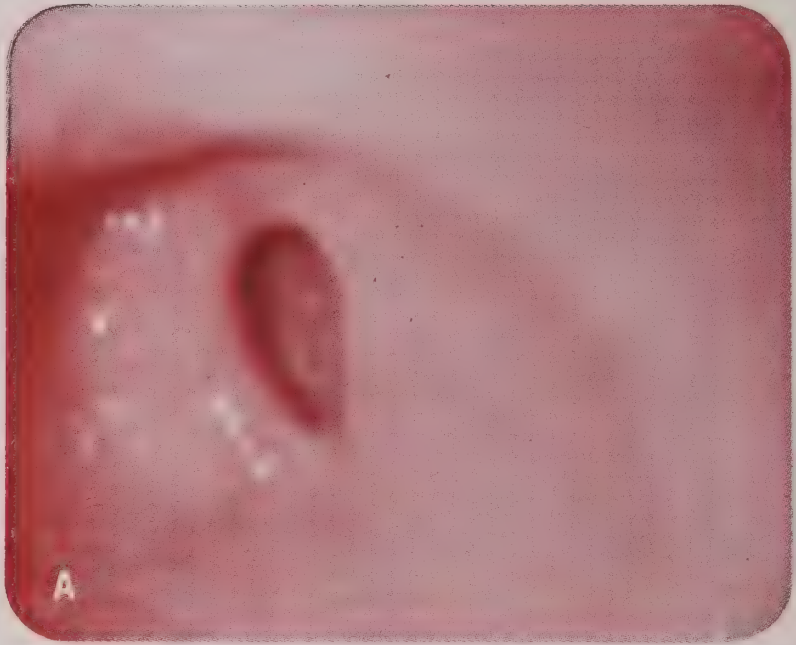
*See Test Your Word Score Page 271.

Reference

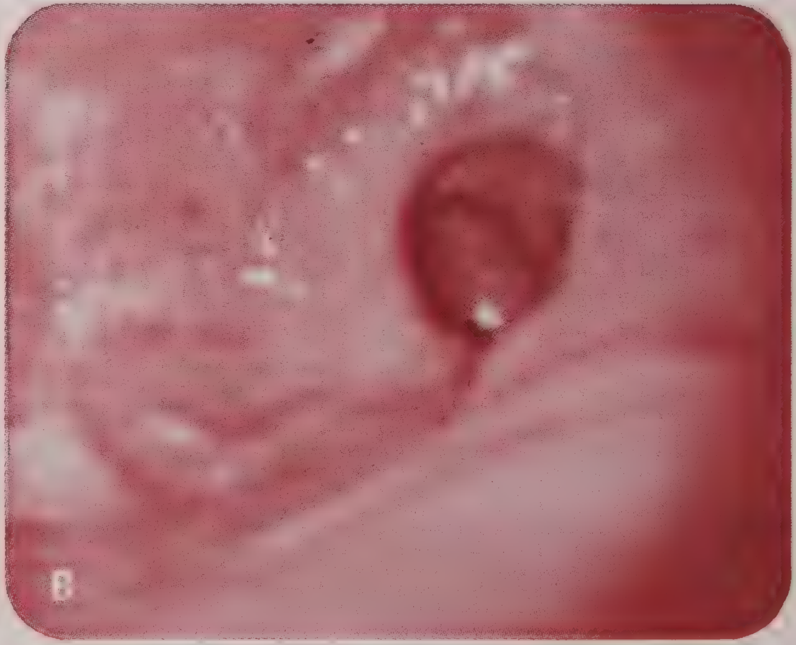
1. Thornell, W. C.: Intralaryngeal Arytenoidectomy in Bilateral Abductor Vocal-Cord Paralysis. Surg Gynec Obstet 95:63, 1952.

Accomplishment

I have enormous respect for anyone who has accomplished anything, anytime, anywhere — Solomon Papper, M.D., Dept. of Medicine, University of New Mexico School of Medicine, Albuquerque.



Which Is Pyloroplasty with Vagotomy?
Which Is Pro-Banthīne?



Photographs—Harry Barowsky, M.D., Lawrence Greene, M.D., and Robert Bennett, M.D., from a Scientific Exhibit presented at the Annual Meeting of the American College of Gastroenterology, Bar Harbour, Florida, Oct. 24-27, 1965.

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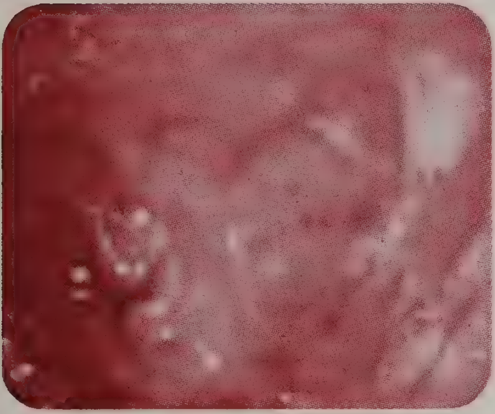

Normal relaxed pyloric antrum; contracted pylorus (pyloric fleurette)

The true anticholinergic values of Pro-Banthīne have never been so graphically realized as they are with the recent development of fibergastroscopy and the intragastric camera.

Pro-Banthīne consistently produces complete relaxation and immobility of the stomach with a dose of only 6 to 8 mg. intravenously. This is less than half the usual dose orally.

Atropine, on the other hand, required 0.8 mg. intravenously, or twice the normal dose, to achieve a similar effect. This high dose of atropine resulted in expectedly adverse side effects.

Pro-Banthīne, in minimal dosage, produces effects similar to pyloroplasty and vagotomy without the disadvantages of permanent postvagotomy sequelae.

The intragastric photograph A is of a patient who has had pyloroplasty with vagotomy. Photograph B is of a patient given 6 mg. of Pro-Banthīne.

Indications: Peptic ulcer, functional hypermotility, irritable colon, pylorospasm and biliary dyskinesia.

Oral Dosage: The maximal tolerated dosage is usually the most effective. For most *adult* patients this will be four to six 15-mg. tablets daily in divided doses. In severe conditions as many as two tablets four to six times daily may be required. Pro-Banthīne (brand of propantheline bromide) is supplied as tablets of 15 mg., as prolonged-acting tablets of 30 mg. and, for parenteral use, as serum-type ampuls of 30 mg.

Side Effects and Contraindications: Urinary hesitancy, xerostomia, mydriasis and, theoretically, a curare-like action may occur. Pro-Banthīne is contraindicated in patients with glaucoma, severe cardiac disease and prostatic hypertrophy.

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Editorials

Bone Marrow Aspiration and Biopsy*

STRIKING AND challenging applications of fluorescence microscopy, isotope techniques and other physical and chemical advances to the study of hematology are now in use. However, morphologic interpretation of the bone marrow retains its fundamental importance to the clinician, hematologist, pathologist, and researcher alike. In 1929 Arinkin[1] proposed aspiration of bone marrow from the sternum for biopsy purposes.

The major growth in the clinical application of marrow aspiration technique has come since the Second World War. Much of the credit for stimulating interest in and encouraging the use of this relatively simple, but valuable, procedure by the local medical community must go to Emil M. Schleicher, Ph.D.* He describes methods for cytologic and histologic preparation of the bone marrow particles which seem rather time consuming. However, they are second to none when one considers the quality of the preparation presented to the pathologist or hematologist for interpretation.

A disadvantage of the technique outlined by Schleicher is the large quantity of marrow desired. Many authors feel that this, of necessity, involves dilution of the marrow sample by sinusoidal blood. A moderate quantity of aspirate is, of course, desirable for the conventional method of bone marrow processing. This involves preparation of Wright's-Giemsa stained smears from the buffy coat plus separation of the bone marrow particles for histologic study.

A complementary method which has recently become a part of our bone marrow aspiration routine is the "supravital" technique as outlined by Sabin,[2] Doan and Ralph.[3] This involves staining of the "living" fluid marrow with neutral red and jannus green. "Supravital" methods are used extensively by the hematology group at Ohio State University.

The routine use of "supravital" techniques often allows a definitive diagnosis to be reported within minutes after the specimen reaches the laboratory. Iron stores can be evaluated without the need for special stains. Frequently, more accurate classification of the acute leukemias can be made. Watching the formation of L.E. cells in vitro is a fascinating experience.

The aspiration techniques are the methods of choice provided a suitable specimen can be obtained. However, in certain situations, not any or only a few bone marrow particles

Continued

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*See page 221.

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# OF CULTURES	YEAR	% EFFECTIVE
6,725	1962	88.6%
5,440	1963	88.0%
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β-Hemolytic Streptococci [2,3,1]		
2,448	1962	89.5%
1,519	1963	95.2%
2,492	1964	96.7%

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Indications: The bacterial spectrum includes: streptococci, staphylococci, pneumococci and gonococci. Recommended for acute, severe infections where adequate sensitivity testing has demonstrated susceptibility to this antibiotic and resistance to less toxic agents. **Contraindications and Precautions:** TAO (triacetyloleandomycin) is not recommended for prophylaxis or in the treatment of infectious processes which may require more than ten days continuous therapy. In view of the possible hepatotoxicity of this drug when therapy beyond ten days proves necessary, other less toxic agents, of course, should be used. If clinical judgement dictates continuation of therapy for longer periods, serial monitoring of liver profile is recommended, and the drug should be discontinued at the first evidence of any form of liver abnormality. It is contraindicated in pre-existing liver disease or dysfunction, and in individuals who have shown hypersensitivity to the drug. Although reactions of an allergic nature are infrequent and seldom severe, those of the anaphylactoid type have occurred on rare occasions. **References:** 1. Isenberg, Henry D.: Health Laboratory Science **2**:163-173 (July) 1965. 2. Fowler, J. Ralph et al: Clinical Medicine **70**:547 (Mar.) 1963. 3. Isenberg, Henry D.: Health Laboratory Science **1**:185-256 (July-Aug.) 1964.

are forthcoming. This is the so-called "dry tap." According to McFarland and Damashek,[4] a "dry tap" may be anticipated in about 6% of marrow aspirates. In the hands of an experienced operator, thoroughly familiar with the aspiration techniques, a "dry tap" is an almost certain indication of serious disease of the marrow organ. Until recently this problem had to be resolved by resorting to surgical trephine with its attendant need for an operating room, probable general anesthesia, and the services of a general surgeon, all of this resulting in added patient morbidity and expense.

Since 1958, several papers have appeared reporting successful results with posterior iliac spine puncture using the Vim-Silverman needle or various modifications of this instrument.[4-7] This technique gives promise of eliminating the need for surgical trephine in most cases.

The specimen obtained with the Vim-Silverman needle is usually 1½ to 2 cm. in length and up to 0.2 cm. in diameter. After a brief decalcification, it can be processed in the same manner as a surgical specimen. The results have demonstrated a specific lesion of the bone marrow in many instances. Silver[6] indicates that in 50% of 266 cases of granulomatous or malignant diseases involving the marrow this biopsy method was the only technique yielding the diagnosis.

The methods of marrow biopsy are simple and in the hands of experienced operators carry virtually no risk. Injudicious use of the sternal aspiration by an inexperienced physician may be hazardous. Bakir[8] recently reported one case and reviewed nine others in which death resulted from through and through perforation of the sternum and pericardium. The fatal outcome in these cases was either demonstrated to be, or clinically suspected to be, cardiac tamponade secondary to hemopericardium.

Many times the study can be demonstrated to be unnecessary by an examination of the peripheral blood morphology. In some situations, other hematologic methods might be productive of more useful information. Also, in an effort to keep the technicians in the hematology section on his side, the clinician is wise if he schedules the procedure as far in advance as possible. In only the most unusual of circumstances should such a biopsy have to be done "stat." As with most other well-controlled laboratory techniques, a bone marrow biopsy interpretation depends upon the quality of the specimen presented to the hematology department.

Walter Subby, M.D.*
Minneapolis, Minnesota

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*Pathology Associate, St. Mary's Hospital, Minneapolis.

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Advances in Scanning

IT IS INEVITABLE that rapid changes in the fields of electronics and radiochemistry should make their impact in the field of nuclear medicine. Just a few years ago, isotopic studies in clinical medicine were by and large related to the study of iodine metabolism by the thyroid. It was only natural that some one should want to plot the distribution of the radionuclide within the target organ, and the thyroid, being the organ most suitable then for study, became the subject of early scanning procedures.[1] Indeed, to

Continued

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this day, the use of the unqualified terms, "uptake studies" and "scanning" by many practitioners in the clinical fields refers to the thyroid gland.

Recent changes, however, have brought about a veritable mushrooming of interest and applicability in the use of radioisotopic scanning. As demonstrated in an accompanying article in this issue by Loken, Telander and Laxdal,* improvements in the art of nuclear medicine are taking place along two major fronts. The first is the development of new radiopharmaceuticals and the second is the emergence of vastly improved detection and recording devices.

The radiopharmaceutical** of choice depends on the organ being scanned, and many different varieties are presently available. However, it is rapidly becoming apparent that in the near future 99m-Technetium may become the universal agent of choice. In the pertechnetate form it is useful for scanning the brain and thyroid. Appropriate modification of the pertechnetate ion will result in agents useful in scanning the liver, spleen, placenta and kidney. Along with its seeming universality are the marked advantages of being able to administer large doses (up to 10 mc.) in order to obtain good counting "statistics" thereby improving the scan image, and still deliver radiation dosage comparable to or lower than that received from agents currently being used.

One of the major drawbacks of present day scanning is the time required to obtain a satisfactory study. The scintillation camera, referred to in Loken's paper, is an example of one of the second generation of scanners and frees the unit from the physical limitations of moving heavy shielded detectors in a rectilinear fashion. Scanning in this mode is performed electronically and reduces the time necessary to a matter of a few minutes — an obvious advantage in clinical practice. This now opens the way for dynamic studies of blood flow, function studies and studies of other processes not heretofore available.

It is apparent that the vast growth in the literature for scanning procedures reflects recent technological and pharmaceutical developments. Looking more closely to home, one finds the number of scanners in use in the state of Minnesota to have risen from 20 in 1964 to 28 in 1965.[2]

Lest the casual reader become too complacent about the high level of performance now obtainable, one has only to reflect upon the fact that "exposure" times now in effect with the best instruments approximate that which was necessary with the roentgen tube shortly after the turn of the century, but a scan image has yet to contain the total number of "bits" of information conveyed on those old glass x-ray plates of the early 1900s.

Marvin E. Goldberg, M.D.
Minneapolis, Minnesota

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*See page 237.
**See Test Your Word Score Page 271.

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Mom says: If you examine your patient too much it might be interpreted as pawing.

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Coronary Blood Flow

We draw our reader's attention to further evidence that nitroglycerine relief of angina pectoris is not explainable by measurable increases in coronary flow (Cohen et al.),* notwithstanding the demonstration of coronary dilatation on arteriograms after nitroglycerine. There is evidence that nitrites produce a fall in systemic and venous pressure, and a decrease in cardiac work, factors which may explain their beneficial effects in the absence of an increased coronary flow.

Cohen and his colleagues propose the use of a test of the effect of nitroglycerine on coronary flow, measured with radioactive rubidium 84, to distinguish between normals, who exhibited an increase in coronary flow, and patients with coronary disease, who did not. The value of this method will be determined by confirmation of these results in much larger test groups.

Rolf Andreassen, M.D.
Minneapolis, Minnesota

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*Cohen, Alberto, Lubs, Eide-Ditmar, Zaleski, Edward J. and Bing, Richard J.: A New Diagnostic Test for Coronary Artery Disease Using A Coincidence Counting System. Minnesota Med 49:17, 1966.

Pyoderma Gangrenosum

Altman and Mopper* present a concise report concerning the rare chronic ulcerative skin disease known as pyoderma gangrenosum which was first described by Louis Brunsting,[1] recently retired as head of the section of dermatology at the Mayo Clinic. Altman and Mopper state that the sulfone drugs, particularly diaminodiphenylsulfone (avlosulfon), are effective in the treatment of pyoderma gangrenosum. The authors agree with Brunsting and his coworkers that the control of any underlying disorder such as ulcerative colitis is important. Altman and Mopper believe that the sulfone drugs do not produce allergic cross reactions with the sulfonamides and appear to be well tolerated in patients who are sensitive to sulfonamides. An encouraging response to the administration of gamma globulin has been reported by Bloom and his associates.[2] Baer and Kopf[3] of the New York University Schools of Medicine believe that patients who have pyoderma gangrenosum may respond well to corticosteroids even after therapy with gamma globulin has failed. The possibility that autoimmunity plays a role in the pathogenesis of the disorder deserves study.

Carl W. Laymon, M.D.
Minneapolis, Minnesota

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*See Minnesota Med 49:22, 1966.

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Neonatal Gastric Rupture*

Rupture of the stomach is probably less rare than the literature would lead one to believe. Few clinicians report their failures except in association with their successes.

While the cause cannot be pinpointed, several mechanisms undoubtedly play a part. Distention, which is present from time to time in all infants, probably is a major factor in thinning out the gastric wall; this compromises the circulation and reduces the stom-

Continued

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*Silbergleit, Allen, and Berkas, Ernest M.: Neonatal Gastric Rupture. Minnesota Med 49:65, 1966.

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ach's ability to resist both the sudden tensions of vomiting, straining, crying and various external forces and the progressive build up of intraluminal pressure from air swallowing and forced feeding. The effect of gastric juices during this set of unfavorable circumstances can only be surmised. Anoxia would seem to augment the effects of compromised circulation.

Curiously, duodenal blockage is rarely associated with gastric rupture. There appears to be some reflex mechanism in this situation, which produces relaxation of the esophagogastric junction and thus permits easy and often effortless eructation of gas and fluid.

Diencephalic lesions are repeatedly mentioned as the cause of gastric ulceration. While this mechanism probably exists, it seems to have little relationship to the massive lacerations so often encountered in neonatal rupture of the stomach.

The trauma of the passage through the birth canal is the most likely source of peak pressure within the lumen of the stomach. It must be assumed that the layers of the stomach rupture at varying tensions and this variation may explain the extensive laceration often encountered with only modest necrosis of the wound margins in an infant who had appeared reasonably normal and vigorous during the first 36 to 48 hours of life.

Silbergleit and Berkas are to be commended not only on their success in solving their clinical problem but also on their efforts to throw light on a very poorly understood entity.

Early detection and immediate operation without unnecessary studies provide the major hope for success in cases of neonatal gastric rupture. The use of a gastrostomy as a postoperative safety vent is to be urged; however, in many of these ruptures there is little area on the anterior surface of the collapsed stomach available for establishing a satisfactory stoma.

Hugh B. Lynn, M.D.
Rochester, Minnesota

Test Your Word Score

Goldblatt phenomenon — *arterial hypertension resulting from partial occlusion of a renal artery,* (page 231).

Pulsus bisferiens — *a dicrotic pulse in which the waves are of nearly equal length,* (page 249).

Arytenoidectomy — *surgical removal of an arytenoid cartilage (one shaped like a jug or pitcher),* (page 259).

Radiopharmaceutical — *a drug or compound in which a radioactive element has been substituted for its stable counterpart, or to which a radioactive element has been attached or added,* (page 267).

Stercobilin — *a reduction product of bilirubin, excreted in the feces and giving them their brown color,* (page 276).

Urobilin — *an amorphous, brownish pigment found in the feces and sometimes in the urine after standing n the air,* (page 277).

Dextrorotatory — *turning the plane of polarization to the right,* (page 277).

Levorotatory — *turning the plane of polarization to the left,* (page 277).

Postictal — *following a seizure,* (page 295).

Hyperrugation — *excessixe wrinkling,* (page 347).

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Side effects: Drowsiness may occur and, rarely, ataxia, usually controlled by decreasing the dose. Allergic or idiosyncratic reactions are rare, generally developing after one to four doses. Mild reactions are characterized by an urticarial or erythematous, maculopapular rash. Acute nonthrombocytopenic purpura with peripheral edema and fever, transient leukopenia, and a single case of fatal bullous dermatitis after administration of meprobamate and prednisolone have been reported. More severe and very rare cases of hypersensitivity may produce fever, chills, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, anaphylaxis, stomatitis and proctitis. Treatment should be symptomatic in such cases, and the drug should not be reinstituted. Isolated cases of agranulocytosis, thrombocytopenic purpura, and a single fatal instance of aplastic anemia have been reported, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity has been reported, usually after excessive meprobamate dosage. Suicidal attempts may produce lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

Usual adult dosage: One or two 400 mg. tablets three times daily. Doses above 2400 mg. daily are not recommended.

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The Physician's Gethsemane

The doctor's responsibility is an onerous, momentous, and sometimes an awesome one. In his profession the physician is not engaged with stable, tangible commodities; instead, he deals with inconstants and imponderables: the unpredictable responses of a diseased or damaged human body. He is faced with solving an equation whose terms are relatively unknown quantities.

It is incumbent on him to exert the last full measure of his professional and humanitarian capacity, not only to achieve the physical recovery but also to assure the emotional and mental stability of the patient and his satellites.

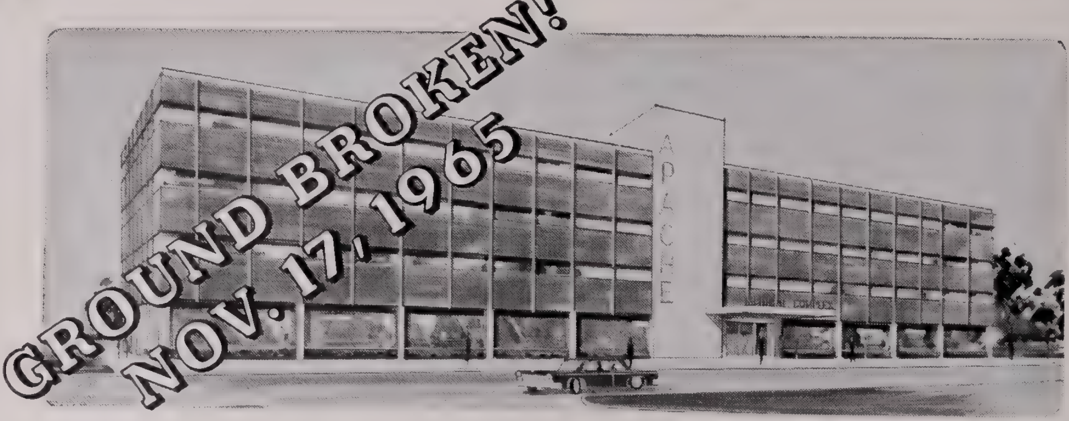
In his single-minded crusade to restore health and conserve life, the physician is a perfectionist and idealist, for whom the best scientific procedure is the only morally admissible one.

During every critical illness or operation there are moments, hours, or sometimes days when a patient floats unsteadily in the balance between life and death; and throughout the patient's delirium the physician searches for the slightest sign of improvement or decline, clues for deciding whether or not to prescribe, to initiate or to defer action, to adopt aggressive or even heroic measures.

He rechecks and reviews; his observations seem incredible; he walks the hall and paces the staff room. To a passing doctor he describes the clinical phenomena; to an anxious intern who has relied on him for previous instructions and advice he relates his findings. He is at liberty to call on any one of his numerous colleagues and this he does. He knows that consultation leads to additional ideas, that it divides his grave responsibility and gives him assurance that he is carrying out the procedures that are in accord with the most modern medical knowledge. If a consultation with one physician cannot resolve the quandary, then another colleague can be called. All physicians are eager to help in restoring life and health to the individual who at the moment is occupying the center of the stage.

In the unfortunate circumstance over which the physician may have had no control, where a series of complications may have arisen in the course of an illness, he is especially challenged; for it is here that his moral and ethical judgment guides him to seek additional advice. If the consultants are essentially unanimous in their decision, no serious problem confronts the attending doctor; and regardless of the outcome of the patient's illness, the unanimous opinion of consulting physicians gives him assurance that liability has been discharged. In the absence of unanimity, however, he stands alone and must remain the final arbiter. If he succeeds he has rendered an invaluable service or he has done no more than was expected of him. If, on the other hand, he fails, he appears to have failed not only his patient but the whole constellation of family, kindred and friends, perhaps even himself and his profession; and failure in no other area of human service is so totally and tragically irreversible as it is in the medical field.

Only when the crisis has passed and the patient is out of danger can the doctor relax, knowing full well, however, that it could have been otherwise. When recovery is assured, he can feel vindicated — but not for long. Tomorrow he will again stand alone beside another patient on the precarious hairline between living and dying — another case to try his mettle and test his morale. His is a lonely job! — Carl O. Rice, M.D.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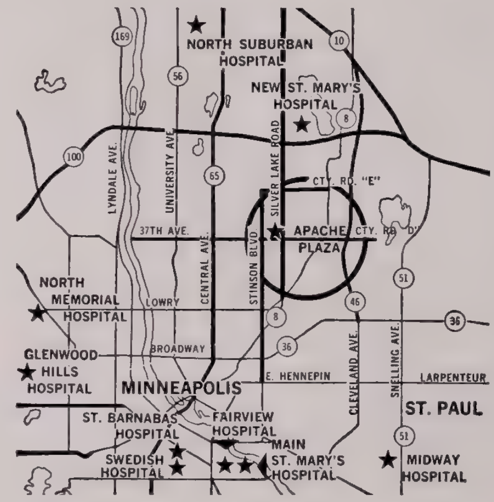
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36
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Our Senior Educators

Cecil J. Watson, M.D.

In 1961, Cecil James Watson, the current Chairman of the Department of Medicine at the University of Minnesota School of Medicine, received the James F. Bell Distinguished Service Award of the Minnesota Medical Foundation and at that time was named Distinguished Service Professor.

Dr. Cecil Watson was born in Minneapolis, Minnesota. His father, James Alfred Watson, was born in Ireland and emigrated to Canada at the age of 16. He graduated in medicine from the University of Manitoba in 1895. For a time Dr. James Watson practiced medicine at Wood Lake, Minnesota. After post-graduate study in diseases of the eye, ear, nose and throat in New York and in Vienna, he returned to practice this specialty in Minneapolis for many years. Dr. Cecil Watson's mother was Lucia Coghlan, also of Irish descent. The Coghlans were early settlers in Minnesota near Wood Lake; it was there that Mrs. Watson was born.

Dr. Cecil Watson grew up in the Kenwood District of Minneapolis and

Continued

attended grade and high school in that locality. He enrolled at the University of Minnesota with the intention of taking premedical training but has indicated on several occasions that his initial interest was actually in English and French literature and writing. For a time he seriously considered a literary career and was not immediately attracted to science. Fortunately his interest in science grew as he took more courses in chemistry. He enrolled as a freshman medical student at the University of Michigan in 1921 and returned to Minneapolis to complete his medical training at the University of Minnesota. Dr. E. T. Bell, Professor of Pathology, had a profound influence on this medical student, and it was under Dr. Bell's guidance that Cecil Watson developed an interest in pathology. He first took a Master of Science degree in that subject. His thesis dealt with periarteritis nodosa, a disease that at that time had not received a great deal of attention. Dr. Watson's first published scientific paper was unique, for he described the earliest recognized case of histoplasmosis in the United States. Darling had reported three cases in the Panama Canal Zone twenty years earlier. As a member of the Department of Pathology, Dr. Watson had performed an autopsy on a woman who had always lived in Minnesota. After detailed study of the case and a review with Professors Hal Downey and Riley, he was able to identify the organisms in the tissue sections.

After graduating from the University of Minnesota Medical School, Dr. Watson obtained a Ph.D. degree in the Department of Pathology under Dr. E. T. Bell's guidance. During his post-graduate training period, he served as pathologist at the Minneapolis General Hospital. His Ph.D. thesis concerned a study of splenic disorders; this study undoubtedly had a significant influence in Dr. Watson's lifelong interest in hematological disorders. In 1928, as a young pathologist, Dr. Watson went to Minot, North Dakota, to a newly-formed clinic. There he had the unusual roles of pathologist, director of laboratories, and also assistant to the internist in the group, Dr. Paul H. Rowe. At that clinic and the immediately adjacent hospital, he served the dual role as resident physician for many hospital patients as well as assuming the responsibility for the duties of hospital pathologist and supervisor of the general laboratory work. The close association with Paul Rowe was an important factor in channeling Dr. Watson's interests into the field of clinical medicine. While at Minot, North Dakota, Dr. Watson continued the studies on urobilinogen excretion that he had started while a pathologist at the Minneapolis General Hospital. In order to further his academic and scientific career, Dr. Watson returned to Minneapolis in 1930 and took advanced courses in organic chemistry. He then went to Munich, Germany, to work in the laboratory of Hans Fischer. While in Fischer's laboratory, Dr. Watson accomplished the crystallization of stercobilin* from an extract of feces. Chemists had long been defeated in an attempt to isolate this substance. This accomplishment further increased Dr. Watson's keen interest in a basic study of the bile pigments as derivatives of hemoglobin catabolism. He stayed a second year in Munich as a National Research Council fellow and, while continuing to work in Fischer's laboratory, managed to find time to attend the medical clinics of the famed Friedrich von Mueller. Thus he continued his interest in clinical medicine while pursuing basic investigations in the field of biochemistry.

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*See Test Your Word Score Page 271.

By 1932, Dr. C. J. Watson had firmly set himself on a career in academic medicine. His initial post on returning to Minneapolis was that of an assistant resident in Medicine at the Minneapolis General Hospital and later at the University Hospital. He continued both basic and clinical studies in the field of bile pigment-porphyrin chemistry while working as a resident at these two hospitals. Somehow he managed to find time to continue work in the laboratory. Without the aid of a great deal of expensive equipment, and certainly without the "benefit" of large research grants, he continued to make significant observations and contributions in his chosen scientific field. It was at this time that he succeeded in crystallizing a urobilin* from human urine and demonstrating that it was identical with the original crystalline stercobilin that could be obtained from feces. His intense interest in the compounds of stercobilin continued throughout the years. In his laboratories he and his students eventually described at least three different members of the urobilin group of substances, the dextrorotatory,* levorotatory* and inactive forms.

In 1932, while still a resident in Medicine at the General Hospital, Dr. Watson was given the responsibility of organizing a course in clinical chemistry and microscopy for the medical students. This he did with great energy and skill. His stimulating presentations of the application of laboratory procedures to the solution of clinical problems had a profound influence on many students. I, for one, was influenced in my decision to pursue a career in internal medicine, by this stimulating young lecturer who presented his material to the junior medical school class in Todd Amphitheatre. The skill of this young physician as a teacher and his accomplishments as an investigator did not escape the attention of the medical school administrators. His rise in the academic ranks was steady, comparatively rapid and certainly well deserved. In 1936, while an Associate Professor of Medicine, Dr. Watson was named as the Director of the Division of Internal Medicine. At that time, the Department of Internal Medicine was under the direction of Dr. J. C. McKinley. Four years later, while continuing as the director in the division, Dr. Watson was named Professor of Medicine, and in 1942 became Chairman of the Department, a post which he holds to this day. At the time that Dr. Watson became a Professor of Medicine and Chairman of the Department of Medicine, the Department was small. The entire staff had no problem assembling in his office, one formerly occupied by Hilding Berglund and located on the second floor of the University Hospital in the Todd Wing just behind the deep X-ray department. Shortly after the outbreak of World War II, Dr. Watson once again found himself participating in a dual professional role, this time as a visiting professor of medicine to the University of Chicago, while continuing his duties in Minneapolis. The Chicago work involved the Manhattan Project. As the Associate Director of the Health Division of the so-called metallurgical laboratory, Dr. Watson would spend two weeks in Minneapolis, two weeks in Chicago. This went on month after month throughout the war. None of us in the department knew the nature of his work and it was

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*See Test Your Word Score Page 271.

Continued

not till the awesome news of Hiroshima was flashed to the world that we became aware of the type of wartime endeavor he had been engaged in. Following the conclusion of World War II, came an era in which many professors of medicine began to take on responsibilities beyond those of their own departments. More and more national committees, conferences and related matters arose to claim the time of prominent men in academic medicine. Cecil Watson did not escape from these added responsibilities; throughout the subsequent years he served on many professional and governmental committees and boards. For a number of years he was the recorder for the Association of American Physicians, later counsellor and, in the year 1960-61, acted as president. He served as a member of the Committee on Medicine and Surgery in the National Research Council as well as on the medical Fellowship Board of the Council. He was an active member of the American Board of Internal Medicine for some years and devoted a great deal of time to the development of their systems of examination. He continues to be an active participating member of such organizations as the Minnesota Society of Internal Medicine, the Central Society for Clinical Research, the American Society for Clinical Investigation and has served in each as the president. In 1959 he was honored by election to the National Academy of Sciences, a distinction not often accorded to investigators in the field of clinical medicine.

Dr. Watson's keen interest in and knowledge of diseases of the liver has long been recognized. From 1942 to 1948, he served as Chairman of the Liver Injury Conference, a series of meetings sponsored by the Josiah Macy, Jr. Foundation. Thereafter he continued as a member of the conference for the next five years. He was asked to assume the position of Director of the Commission on Liver Disease of the United States Armed Forces Epidemiological Board when the commission was founded in 1948. The writer served as Dr. Watson's deputy director and continued to function in this capacity until 1954 when the Commission was reorganized under a different sponsorship.

As the national and international reputation of Dr. Watson grew, more and more demands were made upon his time, including many requests to deliver lectures. One of the earliest and certainly one of the most outstanding requests came when he was asked to deliver the Harvey lecture in New York in 1948. Other outstanding lectureships in which he has participated include the Chester M. Jones lecture at the Massachusetts General Hospital, the George R. Minot lecture for the American Medical Association, and the John Phillips lecture of the American College of Physicians in 1957. Dr. Watson has been honorary lecturer at a number of medical schools in this country as well as abroad. He has been named honorary professor at San Marcos University in Lima, Peru, and was given the same distinction at the University of Chile in Santiago. On a return visit to Chile in 1960, he received the Order of Merit from the Republic of Chile. More recently, in 1962, he received an honorary M.D. degree from the Johannes Gutenburg University in Mainz, Germany.

Throughout these many years of devoted service to the University of Minnesota Medical School, Dr. Watson has achieved the admiration and warm friendship of an untold number of students, interns, residents and faculty associates who have pursued their studies under his guidance or have worked with him.

As an expression of the esteem that his former students and past and present colleagues hold for Dr. Cecil J. Watson, a Recognition Day was held on September 25, 1961. A scientific program with a presentation of original papers by a number of his former students and associates was held in the Mayo Memorial Auditorium. That evening a dinner was held in his honor. The speaker was Dr. William Castle, Professor of Medicine at Harvard University.

The University of Minnesota School of Medicine is fortunate to have had as distinguished an individual as Dr. C. J. Watson to lead one of the major departments of the Medical School from a very small beginning to the current large and productive department that now exists. Dr. Watson's unbounded enthusiasm for clinical and basic investigation continues. Despite the many and arduous duties that confront him, he finds time to counsel and advise those who have the good fortune to work under his guidance. His unselfish devotion to the welfare of the Medical School of the University of Minnesota is recognized and deeply appreciated by the entire faculty and student body.

F. W. Hoffbauer, M.D.*
Minneapolis, Minnesota

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*Posthumous.

Moses as Sanitarian

It corresponds to the reality in both the actual and chronological point of view to consider the books of Moses as the foundation of sanitary science. The more we have learned about sanitation in the prophylaxis of disease and in the prevention of contagion in the modern time, the more have we come to appreciate highly the teachings of these old times on such subjects. Moses made a masterly exposition of the knowledge necessary to prevent contagious disease when he laid down the rules with regard to leprosy, first as to careful differentiation, then as to isolation, and finally as to disinfection after it had come to be sure that cure had taken place. The great lawgiver could insist emphatically that the keeping of the laws of God not only was good for a man's soul but also for his body.

Baas: Outlines of the History of Medicine.

The Superior Man — Confucius (551 to 479 B.C.)

The superior man understands what is right. The inferior man understands what will sell.

The superior man is liberal toward other's opinions but does not completely agree with them; the inferior man completely agrees with others' opinions but is not liberal toward them.

I don't like spinach, and I'm glad I don't, because if I liked it I'd eat it, and I'd just hate it. — Clarence Darrow

The Doctor and Literature

(Continued from page 254).

our anger is satiated. Our victim is ruined and heart broken. And our virtue goes quietly to sleep for seven more years."

Dr. Polidori, accompanied Lord Byron as that unhappy genius dragged through Europe the pageant of his bleeding heart. The faithful doctor tried vainly to curb the excesses of the great romantic poet.

William Shakespeare

William Shakespeare's patron, the Earl of Southampton, withdrew his favor and financial support when he stole the playwright's light-of-love, Mistress Mary Fitton, the Dark Lady of the Sonnets.

Shakespeare bemoans his lot in the opening lines of Sonnet Twenty-nine:

"When in disgrace in fortune and
men's eyes
I all alone bewail my outcast state
and trouble deaf heaven with my
bootless cries
And look upon myself and curse my
fate."

In Romeo and Juliet, Shakespeare gives a rather unattractive description of an apothecary and his shop.

"I do remember an apothecary
Which late I noted in tattered weeds,
with overwhelming brows
culling of simples.
Meagre were his looks,
Sharp misery had worn him to the bone
And in his needy shop a tortoise hung
An alligator stuffed and other skins of
ill shaped fishes;
And about his shelves a beggarly account
of empty boxes
Green earthen pots and old cakes of roses
were thinly scattered to make up a show."

The Apothecary, often known as a herbalist, because he sold love philtres to the credulous, reluctantly sells Romeo a mortal drug.

"Put this in any liquid thing you will and drink
it off
And if you had the strength of twenty men it
would dispatch you straight
My poverty, but not my will consents."

Reverend Edward Keanan
St. Paul, Minnesota

(To be continued next month)

Medieval medicine taught that the soul resided in the liver which secreted vapours and humors.

A hot and dry man was melancholy: melan meaning black, choly signifying bile. A melancholy man suffered from a superfluity of black bile.

A hot and moist man was sanguine and cheerful.

A cold and moist man was phlegmatic or torpid.

The Anatomy of Melancholy by Robert Burton

Curbstone Consultation

Flexor Tendons of Little Finger

QUESTION: Ten months ago both flexor tendons of the little finger were severed and resutured. The finger remains in straight extension with no sign of motion in the middle and distal joints. The extended finger is constantly in the way. What treatment would you recommend at this late stage wherein motion remains only in the metacarpophalangeal joint?

ANSWER: If both flexor tendons were severed and there is a great deal of binding and scarring down, then it may well be that arthrodesis in a semi-flexed position, so that the fingers no longer point in an extended position, would be the best solution. In some individuals in whom the flexibility of the hand is extremely important, and there is no possibility of regaining flexibility in the little finger, the ray resection has been utilized, rather than trying to do any form of reconstruction.

Your question poses the possibility that motion remains only in the metacarpal phalangeal joint, which does bring up the ray resection as the only solution that might be practical in some instances. However, there still is the possibility that a patient would rather try the fixed flexed position before this amputation procedure is done, which can always be performed at a later time.

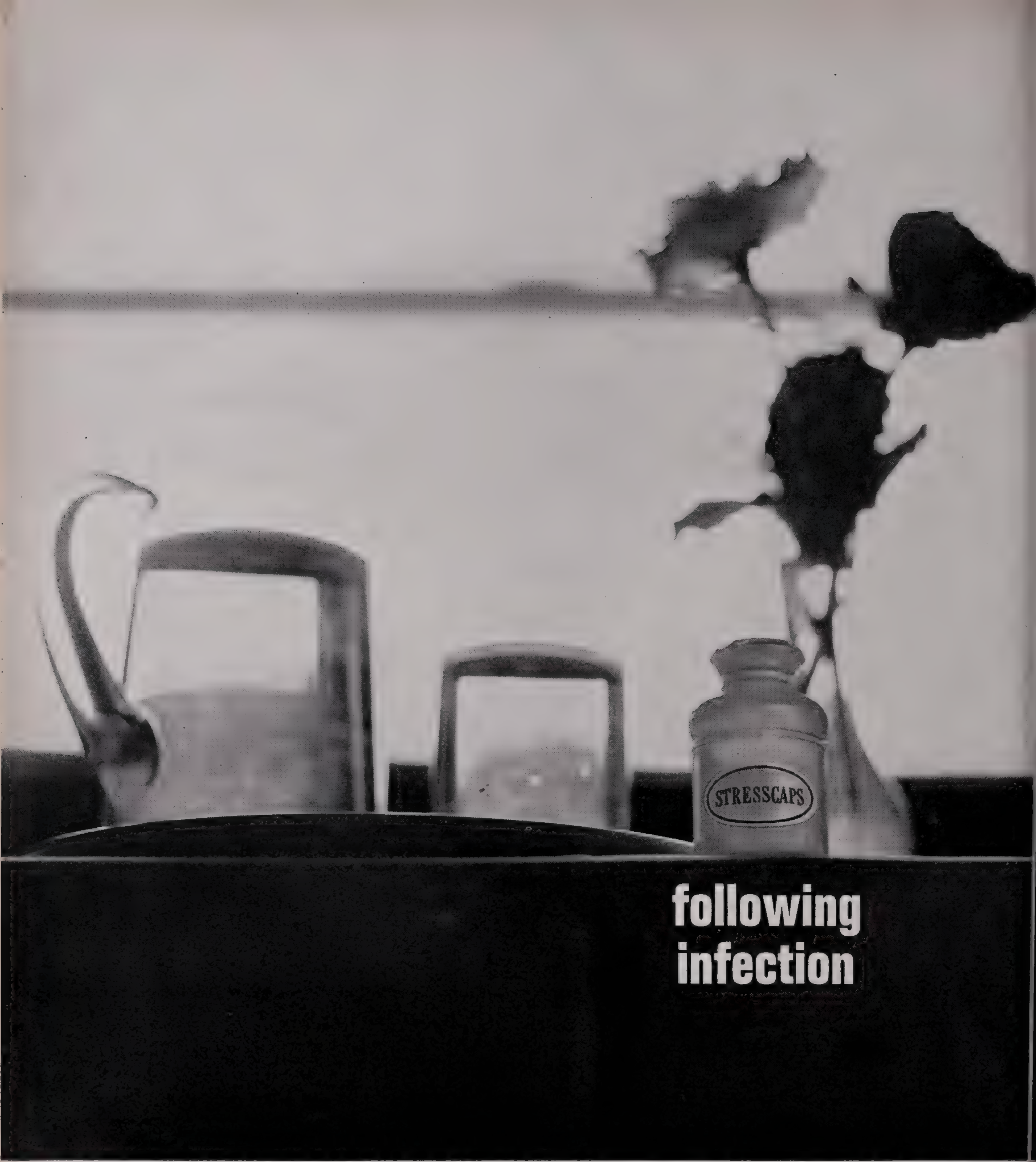
W. E. Miller, M.D.
Division of Orthopaedics, Department of Surgery
University of Miami School of Medicine

Aerosolized Content of Hair Sprays

QUESTION: What dangers exist in the use of hair sprays through inhalation of the aerosolized contents?

ANSWER: The pulmonary changes which have been attributed to inhalation of such sprays have varied from sarcoid-like granulomata to diffuse interstitial fibrosis. The basic agent in hair sprays is an inert substance, polyvinylpyrroliodine (PVP). Experimental work in animals with this chemical has not confirmed the findings said to occur in humans as a result of exposure to this substance. Human studies involving women who were users and nonusers of hairspray showed no difference between the two groups as measured by mid-expiratory flow rates. Observations and studies over longer periods of time will be required before an accurate judgment can be rendered as to effects that might result in persons using hairsprays.

Harold D. Kletschka, M. D.
Syracuse, New York



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Niacinamide	100 mg.
Vitamin C (Ascorbic Acid)	300 mg.
Vitamin B_6 (Pyridoxine HCl)	2 mg.
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The Viewing Box

This 50-year-old white male presented to Hennepin County General Hospital in acute respiratory distress. His symptoms were those of an upper respiratory infection. He had a history of alcoholism and for the past week had been living in a boxcar. On admission the patient appeared acutely ill and in moderate respiratory distress. He had hemoptysis and a white blood count of 4300, of which 79% were PMNs. Of interest is that six months before this admission his chest x-ray was normal.

The admission chest film (Figure 1) is typical of this disease. Notice especially the massive consolidation with bulging fissures due to a volume increase of the affected lobe. Also characteristic is the clear, sharp border of the infiltrate.

What is your diagnosis? (See next page.)

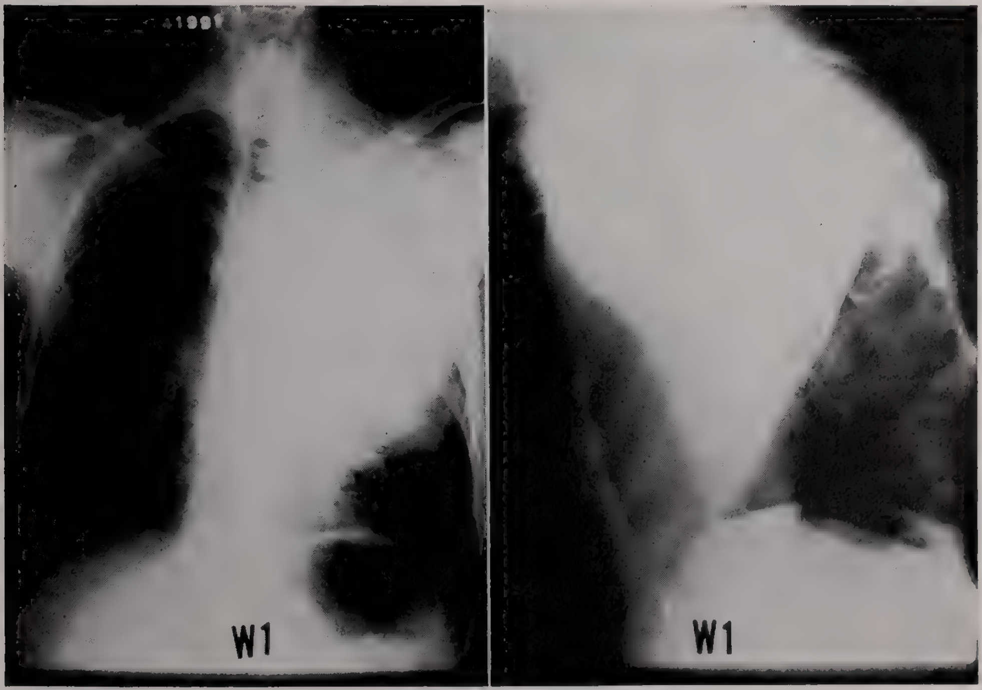

Fig. 1

Diagnosis: Friedlander's (Klebsiella) Pneumonia.

Friedlander's pneumonia, in the acute form, is most prevalent in debilitated individuals. It is most common in males, especially over the age of forty, and there is a high correlation with alcoholism. It is most common in the apical and posterior segments of the upper lobe, and favors the right lung.[3] Friedlander's pneumonia is reported to be responsible for ½ per cent to 1 per cent of all pneumonias in the adult.[1] The etiologic agent, Klebsiella pneumoniae, normally occurs in the respiratory tract from 5 per cent to 25 per cent.[3]

Clinical features of the disease include: acute onset in a toxic individual, thick red sputum, high fever, and pleuritic pain. Leukopenia is common in most infections.

The radiographic picture may resemble other pneumonias. Early abscess formation and cavitation are not uncommon.[4] Because of this, and since the upper lobes are most frequently affected, the differentiation from a tuberculous pneumonia may be difficult.[5] More characteristic are the bulging fissures with a massive consolidation, the border of which is sharp and easily seen.

The patient presented had bacteriologic confirmation of Friedlander's pneumonia. His course was one of rapid deterioration, and in spite of intensive therapy, he died six hours after admission.

Neil R. Hoffman, M.D.
Department Internal Medicine
Hennepin County General Hospital

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Incantations

Closely akin to the power of numbers is that of words. Pliny once says on an incantation employed to avert hailstorms that he would not dare in seriousness to insert its words, although Cato in his work on agriculture prescribed a similar formula of meaningless words for the cure of fractured limbs. But Pliny does not object to the repetition of incantations or prayers if the words spoken have some meaning. In one case where a poultice is to be applied to an inflammatory tumor, Pliny says that persons of experience regard it as very important that the poultice be put on by a naked virgin and that both she and the patient be fasting. Touching the sufferer with the back of her hand she is to say, "Apollo forbids a disease to increase which a naked virgin restrains." Then, withdrawing her hand, she is to repeat the same words thrice and to join with the patient in spitting on the ground each time. Indeed, in another passage Pliny states that it is the universal custom in medicine to spit three times with incantations.*

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*Thorndike, Lynn: A History of Magic and Experimental Science, Vol. 1, p. 92. The MacMillan Company, New York, 1923.

Drive Safely

An "S" curve can turn laughter into slaughter. — Transit News

Fracture–Trauma Conference

Massive Hemorrhage from Pelvic Fractures

It is apparent from clinical experience and a recent autopsy study at Ancker Hospital that massive hemorrhage from fractures of the pelvis does occur and can have lethal consequences.[1] In some instances bleeding is so rapid that blood replacement alone is inadequate. Ligation of hypogastric arteries as a means of treating otherwise uncontrollable hemorrhage from pelvic fractures was first suggested in 1963 by Miller[2] who used it in five patients. Seavers and associates[3] subsequently reported their experience with four patients in whom this treatment had been utilized. This report is a review of our recent experience with patients with fractures of the pelvis and an analysis of the role played by hemorrhage. Results of hypogastric artery ligation in four patients are also given.

Material and Method of Study

The charts and x-rays of all patients admitted to Ancker Hospital with fractures of the pelvis from January 1, 1959, to September 1, 1964, were reviewed. Age, sex, duration of life after admission to the receiving room and mode of injury were recorded. The total number of blood transfusions expressed in units of 500 ml. was tabulated for each patient. The type of pelvic fracture was determined from the x-rays and categorized according to the classification proposed by Key and Conwell[4] and utilized by Milam and Miyakawa[5] in their analysis of urinary tract complication of pelvic fractures.

Type I — Fractures Without a Break in the Pelvic Ring

These include fractures of the wing of the ilium, a single pubic or ischial ramus, fracture of the anterior superior iliac spine, the ischial tuberosity, sacrum or coccyx.

Type II — Fractures with a Single Break in the Pelvic Ring

These include fractures of both rami of one side, separation of the pubic symphysis or separation of the sacroiliac joint.

Type III — Fractures with a Double Break in the Pelvic Ring

Included here are double vertical fractures and severe multiple fractures.

Continued

Type IV — Fractures of the Acetabulum

Using this classification, the mortality rate and percentage of patients with significant blood loss have been determined according to the type of fracture.

Associated Injuries

The nature and extent of associated injuries were tabulated according to criteria employed by Slatis.[6] Thus, lacerations, contusions, and abrasions were excluded from consideration.

Head Injury

Fracture of skull; contusions and lacerations of brain substance; epidural, subdural or subarachnoid hemorrhage;

Chest Injury

Multiple rib fractures, hemothorax, pneumothorax, contusion or laceration of thoracic viscera, and rupture of diaphragm;

Abdominal Injury

Laceration or rupture of parenchymatous organs or rupture of gastrointestinal canal;

Genitourinary Injury

Rupture or laceration of kidney, ureter, bladder, or urethra;

Spinal Injury

Fracture and dislocation of spine with or without injury of spinal cord;

Lower Extremity Injury

Fracture or major vessel injury; and

Upper Extremity Injury

Fracture or major vessel injury.

An attempt was made to assign a primary cause of death in patients who died. This was facilitated by a high autopsy rate (34 of 37 deaths). All deaths directly or indirectly caused by fracture of the pelvis were noted, and this group was further subdivided into those patients who succumbed primarily to blood loss and those who died of other sequelae of the pelvic injury. Both the over-all mortality rate and that due to pelvic fracture were related to mode of injury, type of fracture, and blood loss. Patients with significant blood loss are arbitrarily defined as those who received or should have received blood transfusions.

Results

A total of 196 patients with fracture of the pelvis were admitted to Ancker Hospital during the period studied. Sex distribution was essentially equal with 96 males and 100 females. Distribution by age was fairly uniform from the second through the ninth decades but with only five patients in the first decade and four in the tenth. Average age was 51.4 years with an age range of four to 92 and a median age of 54.

Causative Factors

Traffic accidents accounted for the injury in two thirds of the cases. There were 78 pedestrians struck by cars, approximately 40% of the total. Fifty-two patients or 27% were auto occupants. There were 48 patients or 24% who sustained fracture of the pelvis in falls of a minor nature. This mode of injury involved an older age group as reflected in an average age of 73.1 years and a median age of 79.5. Eighteen patients were injured in a variety of mishaps such as crushing accidents and defenestration of two to four stories.

Mortality Factors

There were 37 patients who died, an over-all mortality rate of 19.4%. Fifteen or 7.7% died primarily from the pelvic injury. Of these, 11 were pedestrians, two auto occupants and two victims of falls.

Severity of Injury

The duration of survival of 37 patients who died reflects the severity of the injuries sustained and the need for vigorous therapy from the outset. Twelve or 32% of deaths occurred within four hours of admission and 22 patients or 59% died within 48 hours. Only one patient died before some treatment could be instituted. Of the 15 patients dying primarily of pelvic fracture, seven or 47% died within four hours and 10 or 67% within 48 hours of admission.

Type of fracture and mortality rate were studied. There were 54 patients with Type I fracture and five deaths, a mortality rate of 9%. Eighty patients had Type II fracture; of these 12 or 15% died. There were 45 patients with Type III fractures, 17 or 38% of whom died. Three of 17 patients with fractures of the acetabulum died, a mortality rate of 18%; none of these deaths was primarily due to the pelvic fracture. In contrast, nine of the 45 patients or 20% with Type III fractures died from their pelvic injuries, as did five of 80 with Type II fractures, a mortality rate of 6%. Only one patient of 54 with Type I fracture died of the pelvic injury, a mortality rate of 2%.

Blood Loss

Significant blood loss, as previously defined, occurred in 77 of the 196 patients. In 63 of these patients blood loss was thought to be primarily from the pelvic fracture (Table 1). Therefore 63 patients, or 32% of the 196 patients, bled significantly from their pelvic injuries. Of these 63 patients, 19 died, a mortality rate of 30%. Of 24 patients receiving more than five units of blood, 13 died, a mortality rate of 54%. In contrast, 119 patients not requiring blood transfusion had a mortality rate of only 8%.

TABLE I
Hemorrhage from Pelvic Fracture

Patients Requiring Transfusion:	63 of 196 = 32%
Mortality Rate of Patients	
Requiring Transfusion:	19 of 63 = 30%
Requiring 1 or 2 Units:	1 of 13 = 8%
Requiring 5 or More Units:	13 of 24 = 54%
Requiring No Transfusion:	9 of 119 = 8%

Continued

In general, the more severe the pelvic fracture the greater was the blood loss. Forty-five patients with Type III pelvic fracture received 335 units of blood or 7.4 units per person, while patients with Type I, II and IV fractures received approximately one unit each (Table 2). Similarly, the percentage of patients receiving blood transfusion was significantly higher in patients with Type III fracture. Thirty of 45 patients with Type III fractures (67%) were given at least one unit of blood, while 15 of 54 (28%) with Type I, 24 of 80 (30%) with Type II, and four of 17 patients (24%) with Type IV fracture required transfusion.

TABLE 2
Type of Fracture and Blood Loss

Type	No. Patients	Total No. Units	Units per Patient
I	54	75	1.4
II	80	87	1.1
III	45	335	7.4
IV	17	16	0.9

Associated Injuries

Associated injuries as defined occurred in 96 patients. The most common associated injury was fracture of the lower extremity which occurred in 54 patients, 18 of whom died; there were no large vessel injuries among these. Chest injuries occurred in 33 patients, 15 of whom succumbed. The upper extremity was fractured in 21 patients, seven of whom died. Fourteen of 16 patients with severe head injuries expired. Fifteen patients had rupture of the bladder or urethra, of whom eight died. Abdominal viscera were injured in 13 patients, seven having ruptured bowel or mesentery, six ruptured spleens, and four minor liver lacerations. There were 10 deaths among these 13 patients, but none was primarily attributed to the abdominal injury. Spinal injury was an associated injury in eight patients, only one of whom died. There were 31 deaths in these 96 patients with associated injury, a mortality rate of 32%. This is in marked contrast to 100 patients with pelvic fracture but no associated injury where the mortality rate was only 6%.

Deaths Attributed to Pelvic Fracture

Closer scrutiny of the 15 patients dying primarily of their pelvic fractures revealed the following data. The average age of these 15 patients at death was 62.8 years as compared to 49.0 years for the survivors. Cause of death in these 15 patients was hemorrhage from the pelvic fracture in nine, fat embolism in two, arteriosclerotic heart disease in two, and severe ileus with electrolyte imbalance in two. Of the nine patients whose deaths were from pelvic hemorrhage, eight were pedestrians and one an auto occupant. Six of the nine died within four hours of admission to the receiving room and eight of the nine died within 24 hours, the ninth dying on the fourth day after admission. Six had Type III pelvic fractures, while three had Type II, and there were none with Type I or IV fractures. Additional injuries were present in eight of the nine, two having a single associated injury and six having two associated injuries. Two of these patients underwent operation, one for repair of the bladder, the other an exploratory laparotomy only; neither had ligation of the hypogastric artery.

Ligation of Hypogastric Artery

During the past year we have had an opportunity to utilize hypogastric artery ligation in four patients with severe hemorrhage from pelvic fractures. The case histories of these patients are reported in detail elsewhere.[7] All four were initially in profound shock and in only one patient was the blood pressure stabilized with initial blood replacement; the other patients had persistent or recurrent hypotension despite continuous blood transfusions. At operation all were found to have massive retroperitoneal hematomas secondary to their pelvic fractures. No effort was made to locate the exact site of hemorrhage other than to verify the integrity of the larger blood vessels. In three patients ligation of the hypogastric artery on the side of the pelvic trauma resulted in abrupt control of the blood loss, while in the fourth patient both hypogastric arteries were ligated before there was a dramatic decrease in the bleeding. Postoperatively there was no recurrence of shock or hypotension in any of the patients. Three patients survived while the fourth died seven days later of fat embolism. Autopsy in that patient revealed that no further hemorrhage had occurred following ligation of the arteries.

Discussion

Although many of the data presented here simply reflect the increasing risk of hemorrhage and death from increasingly severe trauma, some are of definite significance regarding hemorrhage and death from pelvic fractures. Pedestrians have a significantly higher mortality rate from pelvic hemorrhage than do auto occupants or persons injured in falls. This is correlated with the fact that pedestrians sustain more extensive fracture of the pelvis on the average than do patients injured in other ways. This study substantiates the logical hypothesis that the more extensive the pelvic fracture, the greater is the risk of hemorrhage and death from hemorrhage. It also suggests that we can predict with some accuracy from the type of pelvic fracture which patient will be likely to bleed massively. In addition, this study stresses the not-so-well appreciated fact that there is a very high incidence of blood loss requiring transfusion in patients with pelvic fractures, regardless of the extent of the fracture.

Deaths attributed to hemorrhage from pelvic fracture have been shown to occur shortly after admission in nearly all patients. This reflects the fact that hemorrhage can be very rapid and is most likely arterial in such instances. Therefore, if treatment is to be effective, blood must be replaced early and vigorously, and ligation of the hypogastric arteries must be considered.

As Miller[2] has shown, massive hemorrhage in many cases originates from ruptured branches of the hypogastric arteries, these branches lying in close proximty to the pelvis. To find and ligate these ruptured branches at operation is exceedingly difficult, if not impossible, because of their anatomic location and the extensive hematoma which is always present. Ligation of the hypogastric arteries, on the other hand, is a simple procedure. We feel that any patient with pelvic fracture whose blood pressure cannot be restored rapidly with blood replacement and maintained with

Continued

only a few more transfusions, and in whom other cause of hemorrhage has been ruled out, should be considered for hypogastric artery ligation.

Summary

Experience with 196 patients with pelvic fractures over a recent five-year period reveals the over-all mortality rate to be 19.4%. Seven and seven-tenths per cent died primarily from the pelvic injury.

Significant hemorrhage from the pelvic fracture was found in one third of the patients and was by far the leading cause of early death due to pelvic fracture.

Experience with hypogastric artery ligation in four patients suggests this technique is of value in controlling massive hemorrhage from pelvic fractures.

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John F. Perry, Jr., M.D., Ph.D.*
St. Paul, Minnesota

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*From the Department of Surgery, St. Paul Ramsey County Hospital, St. Paul, Minnesota and University of Minnesota Medical School, Minneapolis, Minnesota.

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The Penalty of Overweight

Great eaters and great sleepers are incapable of anything else that is great.
— Henry IV of France

Everyone is a moon, and has a dark side which he never shows to anybody.
— Mark Twain

Who are a little wise the best fools be.
— The Triple Fool, John Donne — 1573-1631

Gardening

The objection to gardening is that by the time your back gets used to it your enthusiasm is gone. — Baltimore Sun

Death is more universal than life; everyone dies but not everyone lives. — A. Sachs

Tumor Conference

Squamous Cell Carcinoma of the Anus

Squamous cell carcinoma of the anus accounts for about four per cent of all anorectal malignancies.[1,2] It must be differentiated from such benign lesions as thrombosed hemorrhoids, condylomata, chancre, nonspecific ulcers or tuberculosis. Malignant lesions of the anus also include malignant melanoma, lymphoma, carcinoid and anorectal adenocarcinoma. Epidermoid cancers arising just above the pectinate line tend to have a more varied histologic structure and a greater malignant potential than those arising from the anal margin.[3]

Aside from local invasion, the tumor spread follows the lymphatic drainage of the anal canal. It involves the lateral pelvic nodes via the inferior and middle hemorrhoidal plexus and the preaortic nodes through the superior hemorrhoidal plexus. Portal and systemic hematogenous dissemination occurs by this route. Metastatic spread to the inguinal lymph nodes follows either the hypogastric pathway or directly through perineal lymphatics. Squamous cell carcinomas of the anus, which are located distal to the pectinate line, are more likely to metastasize to inguinal nodes than those which originate at or above the pectinate line.

Case Report

A 72-year-old white veteran was admitted on July 29, 1963, with the chief complaint of "painful hemorrhoids" of three months' duration. The patient was known to have had large hemorrhoids for at least twenty years. Since the onset of pain, he had also noted some bleeding from the anus and had become aware of a growing mass.

He was well nourished and there were no abnormal abdominal findings. In addition to several skin tags, an edematous mass with surface maceration was seen around the posterior anus. Anoscopy revealed immobile internal hemorrhoids. The prostate was smooth and moderately enlarged. The lobulated posterior anal mass did not involve the pectinate line. The inguinal lymph nodes felt normal. A punch biopsy of the anal growth revealed infiltrating squamous cell carcinoma.

On September 26, 1963, an abdominoperineal resection with wide perineal and pelvic margins was performed. The preaortic, common iliac, external iliac and hypogastric nodes were removed en bloc. Eleven normal lymph nodes were identified and no metastases were found. The tumor measured 6 cm. x 4 cm. x 2.5 cm. and originated distal to the pectinate line. The nearest line of perineal resection was 3 cm. from tumor tissue (Figure 1). The postoperative course was stormy and complicated by thrombo-

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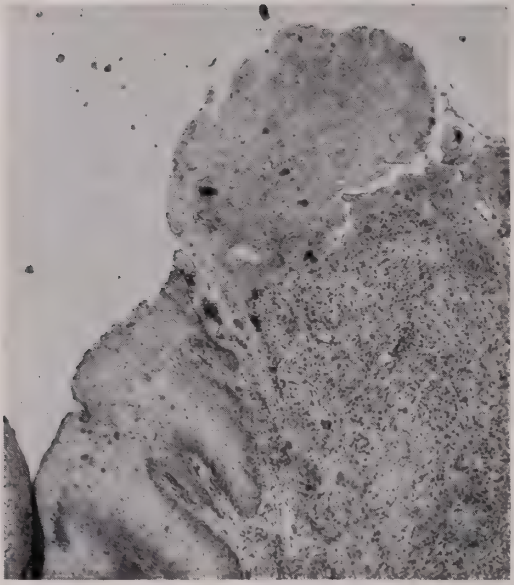

Fig. 1 — Specimen of abdominoperineal resection. The anal skin gives way to an exophytic, infiltrating, well differentiated squamous cell carcinoma.

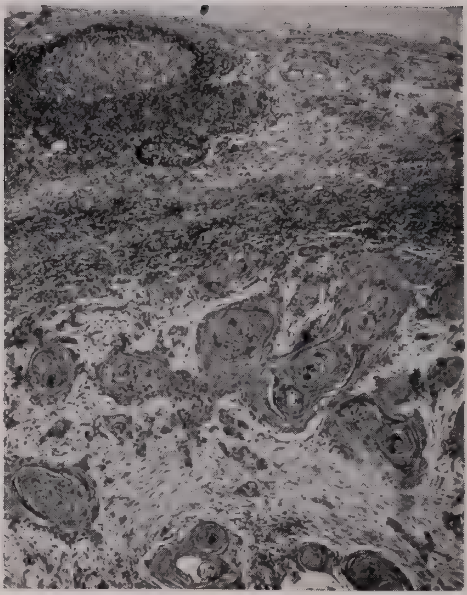

Fig. 2 — Inguinal lymph node, largely replaced by squamous cell carcinoma.

phlebitis in the left leg. When this subsided, a persistent enlarged left inguinal lymph node was noted. Excision biopsy showed squamous cell carcinoma within a lymph node.

On March 4, 1964, a left radical groin dissection was performed, using the technique of Byron et al.[4] Thirty-four lymph nodes were identified. Squamous cell carcinoma metastases were found in nodes of the lower triangle of Scarpa (Figure 2) and in subcutaneous nodes below the inguinal ligament. The recovery was delayed by wound dehiscence and by marked lymphedema of the left leg. The patient was discharged on June 5, 1964, and has been followed at regular intervals. At this time, two years after resection of the primary tumor, there is no demonstrable recurrence of cancer and the lymphedema of the left leg has largely subsided.

Comment

The management of squamous cell carcinoma of the anus is controversial. Local excision or treatment by irradiation has been disappointing.[1,6] An en-bloc resection of the tumor and its primary areas of lymphatic drainage necessitates an abdominoperineal resection and bilateral radical groin dissection in continuity with the tumor. In view of the increased mortality and high morbidity with this radical procedure a "watch and wait" attitude now prevails.[2] The abdominoperineal resection is followed by groin resection only when inguinal metastases have appeared. Sedgwick and Wainstein[5] oppose this approach and state: "When large positive inguinal nodes are present, groin dissection adds nothing to the survival rate and is contraindicated." Stearns[6] found that only 6% of patients with anal carcinoma would have benefited from prophylactic groin dissection. However, in his group of thirteen patients who had been treated with abdominoperineal resection and with groin dissection after an interval, five were well two to six years after resection of the primary tumor. Our patient had a stormy and prolonged recovery from an abdominoperineal resection. When inguinal metastases became apparent after a four months' interval, a radical groin resection was performed. This major procedure was also followed by grave complications. The elderly man may not have survived both operations had they been performed simultaneously.

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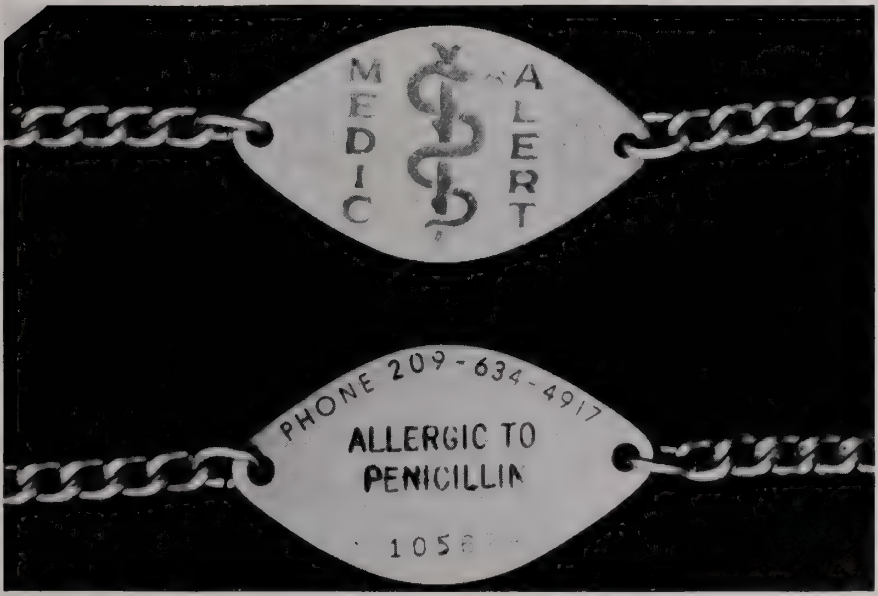

Be alert to these emblems!

One of the best rules in conversation is, never to say a thing which any of the company can reasonably wish had been left unsaid. — Swift

A coquette is a woman without any heart, who makes a fool of a man that hasn't got any head. — Mme. Deluzy

I think there is only one quality worse than hardness of heart and that is softness of head. — Theodore Roosevelt

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Neurological Conference

Management of a Convulsive Disorder*

Student Doctor Guy O'Grady

This 38-year-old married woman has had seizures since 18 years of age. Her first seizure occurred on the same day that she began a new job and consisted of a sudden loss of consciousness, resulting in her falling down several stairs. There was no aura, and the patient was told that she lay motionless during the period of unconsciousness. Since that time she has had perhaps 20 to 30 seizures, sometimes with an interval of one to two years between episodes. More recently, however, she has noted an increase in the frequency of the attacks and has had five seizures in the last six months. They are particularly prone to occur during menstrual periods or when she is excited; for instance, she had a seizure on the day after Christmas, while entertaining some of her friends. This attack was not preceded by an aura. Her sister described the patient as suddenly falling to the floor with clonic movements of both legs, and then lying quietly for about five to 10 minutes before regaining consciousness. She could give no further description except that the patient did not bite her tongue, nor was she incontinent of urine or feces during the episode. The patient commented that she often did not feel well for several days after a seizure. During a typical postictal** state, she experiences weakness, headache and marked depression. She has taken phenobarbital 30 mg. q.i.d. after each seizure but usually discontinues the medication within a few months.

Past History

The patient had pulmonary tuberculosis in 1951, at which time she was hospitalized for 17 months and treated with streptomycin and para-amino salicylic acid. Chest films have showed no change since the time of dis-

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*Sponsored by the U. S. Public Health Service Grant N2502A63. These conferences are an integral part of the Comprehensive Clinic Program at the University of Minnesota Hospitals. The pediatrics conferences are held every Wednesday from 1:00 to 3:00 p.m. The adult conferences are held every Thursday at 4 p.m. Co-ordinators for the project are Dr. Charles Branthaver and Dr. Edward De Foe in Pediatrics, and Dr. Robert Soll, in Adult Neurology.

Held on Wednesday, April 15, 1965, 4 p.m.

**See Test Your Word Score Page 271.

Continued

charge from the sanatorium, and a recent gastric washing revealed no tubercle bacilli.

The patient was married in 1963 and became pregnant in January, 1964. Preeclampsia developed and she was placed on two medications to combat her increasing hypertension. No seizures occurred during the pregnancy, but in late September the patient delivered a stillborn. Consequently, she has been very concerned about the advisability of future pregnancies.

There is a strong history for gout among the patient's relatives; three of her mother's 10 siblings had clinical gout.

Laboratory Data

Physical examination of the patient was entirely normal. The laboratory data revealed a normal blood count and urinalysis, a two-hour postprandial blood sugar of 96 mg.%, a serum uric acid of 5.8 mg.%, and a normal electrocardiogram. The waking electroencephalogram showed bursts of 4 to 5/second spike and wave complexes superimposed on a mildly abnormal background only during hyperventilation. It was felt that the record suggested a centrencephalic convulsive disorder.

The patient was seen subsequently in Neurology Clinic where a thorough neurological examination confirmed the normal physical examination. Dilantin 100 mg. b.i.d. and phenobarbital 100 mg. h.s. were recommended to be taken indefinitely. It was felt at that time that the patient probably had grand-mal seizures.

Dr. Robert Soll*

Dr. Wilson, is there anything you can add about her seizure history?

Dr. Louis Wilson**

Yes, the patient's older sister has petit-mal attacks, characterized by short epidoses of amnesia. I think they are under control now, however.

Dr. Soll

Frequently, as patients grow older, their petit-mal attacks may be replaced by major motor seizures.

The Patient Enters the Conference Room

Dr. Soll

Would you describe to us how you feel just before a seizure occurs?

Patient

I don't think I actually know, except for the last attack I had. I think I probably felt it coming on, so I started for the bedroom. When it occurred, I was between the kitchen and dining room door. I felt a strangeness possibly.

Dr. Soll

How do you feel after you have had a spell?

Patient

I know that just minutes after I have had one, I am talking, but I remain groggy and also depressed for the rest of the day. I think I am just plain disgusted that I had another attack.

---

*Pediatrician and Moderator, University of Minnesota Hospitals.

**Referring physician.

Dr. Soll

How do you feel about having another child?

Patient

I think I would like to have one, of course, but no one can be certain of having a well baby.

Dr. Soll

Since we have given you more medication this past month than you have had for a number of years, have you felt any different?

Patient

Yes, I am much more drowsy. I could sleep 15 hours out of 24.

Dr. Soll

It will probably be some time before we really know how effective this medication will be in preventing your seizures, since they have been relatively infrequent in the past.

Dr. Richard Magraw*

I am not sure that I understand why you decided to check into your seizures now.

Patient

I asked Dr. Wilson about it, and he thought it would be a good idea to be certain there wasn't any brain damage or a brain tumor. After I had one of the seizures at home I decided to find out if anything more could be done.

Dr. Magraw

Had there been any change in the seizures?

Patient

No.

Dr. Magraw

Why did you want to do something about this now rather than last year or next year? What was the last straw that made you decide?

Patient

I just felt that probably there was something else that could be done so I wouldn't be having the seizures any more. I had been taking phenobarbital and I felt that maybe there might be another drug that I could be taking. Of course, I had just had the baby recently.

Dr. Magraw

Did you think that there might be some connection between the two?

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*Director, Comprehensive Clinic.

Continued

Patient

Yes.

Dr. John Brantner*

Did your last seizure occur shortly after your first visit to the University?

Patient

The very last one that I had was at that time, yes.

Dr. Soll

Have you ever noticed any relation between your seizures and your periods?

Patient

Yes, the seizures usually occur at the time of my period. That is why I thought it may have had something to do with my pregnancy.

Patient Leaves the Room

Dr. Magraw

There is an old question and one that should always be asked in medicine: Why does the patient complain? She has had seizures for 20 years, so why should she inquire more about them now. In this instance, it clearly appears that she is relating the control of her seizures with her physical fitness and her likelihood of having a successful pregnancy.

Dr. Brantner

I asked about the date of her last seizure because several people have suggested that one of her prolonged postictal symptoms was a mild depression. I have the results of her Multiphasic. Although I did not notice any evidence of depression in the patient myself, it did appear in the Multiphasic. She had a seizure on March 16. The Multiphasic which was taken 14 days later revealed a mild depression and anxiety; otherwise, it was normal. It did not indicate significant hypochondriacal concern, but rather only a reasonably normal number of physical complaints for a patient. She is an intelligent woman, with an IQ of 120 (the lower range of the superior level). Testing her was a little difficult, as it sometimes is with some intelligent people who don't understand why they are asked to answer simple questions and to perform easy tasks. On visual motor coordination tests, she shows no signs of cerebral dysfunction. The Porteus Maze was a little lower than might be expected with her level of intelligence. This might be related to the EEG findings, or more likely, it shows that she is a person who can be flustered easily; for example, she made one minor mistake that she should not have made, after which her performance deteriorated considerably. She repeated the mistake a second time and became even more flustered.

Miss Helen Kretchmer**

I interviewed the patient during her second clinic visit. She was very responsive to everyone with whom she talked. She and her husband were married in August, 1963. He had been married previously and has two children, a boy 17 years old and a girl aged seven. The patient seems happy with her marriage and enjoys the children. Her only pregnancy terminated in a stillbirth, but she would still like to have a child of her own.

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*Assistant professor, clinical psychology, University of Minnesota Hospitals.

**Supervisor and assistant professor of social service, University of Minnesota Hospitals.

After graduation from high school the patient had one year of business college before beginning work in the office of a physician. She remained there for 17 years, until the doctor retired. The patient's husband is a carpenter for a construction company, earning approximately $180 a week before deductions.

Although the patient's sister, who has seizures, is doing well on medication, the patient continues to worry about her own condition. She is anxious to have another child, but the possibility of toxemia or a recurrence of her lung condition has caused her much concern. She also thinks there may be an increased likelihood of seizures in her child. The prospect of having a child is painful for her to discuss, but I believe she would benefit by consultation with an obstetrician regarding future pregnancies.

She is also concerned over advice that she should not drive until complete control of her seizures is attained. The 17-year-old boy has never seemed willing to drive although he passed his driver's training; so it is difficult for her to manage when her husband is away.

The evaluation here has been anxiety-provoking for the patient and she hopes to be referred back to Dr. Wilson for care as soon as possible. She does not like to come to the city alone and seems anxious because her husband is not here with her. The patient's sister said that she was overly fearful even about members of her family knowing that she has seizures; however, the sister feels that she has carried this to extremes.

The patient is paying for medical care here on a per-diem or reduced-fee basis. There are no local agencies active.

The patient has a good relationship with her physician, Dr. Wilson, and he has given her supportive help through previous illnesses. With adequate seizure control, her anxieties may be reduced, but she will need more help in understanding her condition and deciding whether to go through another pregnancy, which she both desires and fears.

Dr. Soll

I would like to ask Dr. Charles Tietz to comment on the patient's obstetrical history and then give us his recommendation regarding any future pregnancies for the patient.

Dr. Charles Tietz*

I have several questions that I would first like to ask. When did she develop preeclampsia?

Dr. Louis Wilson

It was after the pregnancy was approximately 20 weeks. She had albuminuria.

Dr. Tietz

Did she seem to respond to treatment fairly well?

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*Medical fellow, obstetrics and gynecology, University of Minnesota Hospitals.

Continued

Dr. Wilson

Yes, her pressure was as high as 160/110, and at the time of her last office visit just before she delivered, it was 148/72. It took several weeks to return to normal.

Dr. Tietz

I think the problem that a woman of this age presents is whether toxemia is superimposed upon chronic hypertensive disease or whether she is developing arteriosclerosis. The history that has been given suggests that she simply had preeclampsia, though this is difficult to establish, really, because we have had fetal losses when the maternal blood pressure was in the range of 130/90 as well as with blood pressures in the range of 170/120.

I see no reason why she shouldn't have another pregnancy, particularly if she is normotensive at the present time. I would lean toward watching her more closely than I would if she had a previously normal pregnancy. Usually patients who will not do well are those who are chronically hypertensive, having a pressure in the vicinity of 170/110. They will either abort very early or have early second trimester losses. It is very possible that her stillbirth was not due to preeclampsia. She lost the baby at about 37 weeks.

Dr. Wilson

She hadn't felt any movement for four days before delivery and the fetal heart tone was not present then.

Dr. Tietz

The cause of a stillbirth may go without explanation in as high as 80% of the cases. Occasionally there are obvious causes such as diabetes, erythroblastosis or severe toxemia. Nevertheless, the reason she lost the baby may not have been due to the blood pressure at all. She doesn't have much of a reproductive career remaining, but if she wants a child, one could watch her closely and probably even deliver her early, particularly if she showed signs of not responding well to therapy. An unexplained stillbirth is the usual situation. Most patients with this kind of story do well in their next pregnancy. Of course, this patient's age is against her, plus the fact that she has had preeclampsia. I would say the chance of her getting recurrent toxemia with this next pregnancy would probably be somewhere in the neighborhood of two to three times greater than an ordinary person. The fact that she didn't have any seizures during her pregnancy is in her favor.. About 30% of women who have seizures and become pregnant will have an increase in seizure frequency. Another 30% will have no change at all and the remaining ones will improve.

Dr. Soll

Hormonal changes can aggravate the seizure condition because of salt and water retention. The usual anticonvulsant medications such as barbiturates and dilantin are usually well tolerated during pregnancy.

Dr. Tietz

Other than the gingival changes in the mothers, which are infrequent, we haven't found any serious side effects to the usual anticonvulsant medication. I suppose that her next pregnancy would be extremely important if there is such a thing as a premium baby.

Dr. Wilson

I am not certain that she really had wanted to get pregnant initially, but she was very disappointed that she didn't have this child. Once she was pregnant she felt wonderful.

Dr. Soll

Approximately 80% of all patients with seizures can achieve virtually complete control. Here at the University it is quite likely that we see mostly problem cases in which control hasn't been achieved; consequently, many of our patients do comprise a relatively small selected group who continue to have seizures.

The goal for which we strive in using anticonvulsant medications is optimum control of seizures with the least amount of sedation. Drowsiness is probably one of the most common side effects, and this would be expected, since most anticonvulsants are depressant in nature.

Barbiturates comprise probably one of the largest groups of anticonvulsant medications and have virtually replaced the bromides which now are seldom used except in very unusual circumstances. The main area of usefulness of the barbiturates is for treatment of grand-mal and psychomotor seizures. Phenobarbital is one of the most commonly used in this group, being the safest as well as the cheapest.

Mephobarbital or mebaral is simply a methylation of the basic phenobarbital molecule. Much of it undergoes demethylation in the body to phenobarbital, accounting for at least part of its anticonvulsant activity. On a weight basis, it is not as potent as phenobarbital, since 60 to 100 mg. of phenobarbital would be equivalent to 200 mg. of mephobarbital in suppressing seizures. One interesting aspect concerning the use of barbiturates is that they are fairly long-acting; consequently, a single or twice daily dose produces almost as good seizure control as multiple divided daily doses. Often this feature can be used to advantage by administering the barbiturate at bed time when drowsiness is a desirable side effect. The patient is then relatively more alert during the day.

Mysoline, the chemical name of which is primidone, is very closely related structurally to the barbiturates but is not a true barbituric acid, since it does not have the acid radical. This drug is also commonly used in treating grand-mal and psychomotor seizures. When first starting a patient on mysoline, it is important to remember to start with very small doses in the range of 50 mg. two or three times daily. Subsequently the dose may be gradually increased to 250 mg. three times daily. This will minimize the likelihood of vertigo, drowsiness or gastric upset.

Diphenylhydantoin sodium, commonly known as dilantin, has been used since 1938 and ranks next to the barbiturates in being one of our most potent drugs. It is a very good drug from the standpoint that it produces minimal sedation with probably as great an anticonvulsant potency as any medication we have available. Using a combination of dilantin with one of the barbiturates such as phenobarbital or mebaral is a very common

Continued

practice since they seem to supplement each other in controlling seizures. Approximately one third of patients who take dilantin for a long period of time may develop hyperplasia of the gingivae. This is not a serious complication, however, and is almost never a good reason for discontinuing the drug, as good dental hygiene will usually control this problem, and an occasional patient who develops a severe hyperplastic reaction can be treated by the dental surgeon if necessary. There are two commercial preparations in which dilantin is combined together with a barbiturate. Mebroin is a tablet containing both mebaral and dilantin. Phelantin is a capsule containing phenobarbital, dilantin and desoxyephedrine. In general these are more expensive in this form but have the advantage of reducing the number of pills a patient must take each day.

For petit-mal seizures, tridione is one of the most commonly used anticonvulsants. This type of seizure is much more difficult to control as a rule than most other seizures, and tridione will control only about one third to one half of patients with petit-mal seizures. If tridione fails to help, paradione may be substituted. Besides the diones there is also another group of drugs used in the treatment of petit-mal seizures, called the succinimides, which include Celontin, Milontin and a more recent addition, Zarontin. Tridione is used in doses of 300 to 600 mg. four times daily. Again one should start out with smaller doses, gradually increasing until the optimum dose is achieved.

Some drugs can be categorized into an adjunctive group of anticonvulsants. The carbonic anhydrase inhibitor, Diamox, may have an anticonvulsant activity by virtue of its diuretic activity as well as its ability to induce metabolic acidosis. This latter may be somewhat similar to the metabolic acidosis produced by a ketogenic diet commonly used at one time. Another medication, Elipten, has been used as a supplemental medication to the standard anticonvulsants particularly in the treatment of refractory seizures. The mode of action of this preparation is unknown. Side effects are very few; a rash may occur in some cases, although this usually clears spontaneously within a few days. Finally, there is the group of amphetamine drugs which are used chiefly to counteract sedation produced by the barbiturates or other anticonvulsants.

Significant toxicities resulting from the anticonvulsant drugs appear infrequently. Rashes are probably one of the most common side effects shared by almost all of these medications including the hydantoins and barbiturates. One of the first hydantoin drugs which actually preceded dilantin was nirvanol. Its use was associated with a very high incidence of fever, lymphadenopathy, and various types of blood dyscrasias. Mesantoin, which is simply a methylation of nirvanol, produces many of the same complications and is not often used clinically. Although in the same group of drugs, dilantin fortunately has an extremely low incidence of similar side effects.. Phenurone is sometimes used for psychomotor seizures; but this is a very dangerous drug which should be employed only in those instances when there is no other possible medication available to control the seizures.

Dr. Richard Magraw

This patient really has had very few seizures. Much of her difficulty may be that she has a pretty damaged concept of herself. She is the kind of person who is driven by the feeling of not being worth very much, and this is the attitude that has made her such an efficient office nurse. Over the years, these people are prone to have recurrent feelings of depression. She has already told us some of the things that bring this on, for example, her seizures, having had tuberculosis, the loss of a child, etc. When she advances into the involutional period, she will be even more inclined to this type of reaction.

Dr. Soll

We can strive to achieve complete seizure control within the next year or two. This may help her to increase confidence in herself. The regimen of dilantin and phenobarbital that she is now receiving should be well tolerated, and it is very unlikely that these medications would interfere with any future pregnancy.

Dr. Magraw

I feel that the lesion which needs even greater attention is her poor "self" concept. I am reminded of a young girl who came to the University ostensibly to have her esotropia treated. This was her complaint, but when asked what really bothered her, she said "The kids at school call me a 'cross-eyed' bean pole." Similarly, obtaining control of her seizures should be helpful for the patient, but she will continue to be vulnerable to anything that comes along which might indicate a flaw in the weave, so to speak.

This is a classic example of a patient who presents to you a very obvious handle by saying, "Here's my problem, seizures." However, it is much more complex than that. There is a Norse legend about Loki,* a Norse god, challenging Thor to lift a certain cat. Thor strained to pick the cat up, but found that it was really the disguised head of a mythical serpent which had twined itself about the earth three times. As a result he had been trying to lift the whole globe and not just the cat.

I mention this story because problems often come to us in this way. We may try to avoid becoming involved by interpreting the patient's complaint in the most literal sense. Yet it is better for the patient, from the standpoint of his recovery, to understand the whole problem and not only the superficial difficulties.

Discussing these various feelings which she has concerning herself with these individuals, particularly Dr. Wilson, would be beneficial and can serve to reinforce her "self" concept.

Conclusions of the Conference

1. Control of the patient's seizures should be obtained by appropriate regulation of her anticonvulsant medications.
2. The patient should be reassured that her convulsive disorder very likely will not adversely affect a future pregnancy.
3. Although there is a possibility of recurrent toxemia with another pregnancy, it is less than with her first pregnancy and should not deter her from having a child.
4. The patient should be helped in improving her own "self concept" through discussions, primarily with her family physician.

Robert Soll, M.D.
University of Minnesota

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*See page 304.

Continued

Participating in the conference were Dr. John Brantner, Assistant Professor, Clinical Psychology; Miss Helen Kretchmer, Supervisor and Assistant Professor of Social Service; Student Doctor Guy O'Grady; Dr. Charles A. Tietz, Medical Fellow Obstetrics & Gynecology; Dr. Richard Magraw, Director, Comprehensive Clinic; Dr. Louis Wilson, referring physician and Dr. Robert W. Soll, Neurologist.

On Lifting a Cat*

The Scandinavian Eddas treat us to some stirring tales of the old Norse gods: not only their heroic triumphs but their humiliating defeats as well. It is precisely because these pagan gods were represented as neither omnipotent nor invincible that we moderns, like the early Norse whose fertile and flamboyant imagination produced them, can relate warmly to them. Like ourselves they were humanly fallible.

One of these gods, of the Aesir** membership, was the valiant and redoubtable Thor (Thursday is his namesake), who always carried a mighty hammer — and seldom failed to use it upon the slightest pretext — or even with no provocation at all.

On one of Thor's numerous jaunts to alien territories to show off his extraordinary strength and skill, he proceeded to Giantland (Utgard) where Loki† reigned. Knowing Thor's vanity and presumptuousness and thinking to show him up before the assembled Giants in the banquet hall, Utgard-Loki challenged him to demonstrate his prowess by lifting a large gray cat which suddenly leaped into the middle of the hall, apparently from nowhere. "Nothing to it!" thought Thor as he bent and seized the cat beneath its stomach. But though the cat's back arched upward with each tremendous endeavor by Thor to lift the animal, only one paw was finally raised slightly off the floor on Thor's last and most prodigious effort. On Thor's departure Utgard-Loki confided to his discomfited guest that the mere cat had not been a cat at all but Midgard, the formidable World Serpent, who in old Norse cosmography encircled the earth with its tail in its mouth. And furthermore, added Utgard-Loki: when the cat's paw had been slightly raised off the floor, all the Giants had been aghast and had trembled as Midgard's mouth and tail momentarily separated under the strain, thereby jeopardizing the solidity and cohesiveness of the very globe itself.

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*See page 303.

**Aesir, the pantheon of Norse gods, headed by Odin.

†Not to be confused with Loki, spirit of evil and mischief, the 'enfant terrible' of the Aesir.

Progress Note

The patient was asked if he had passed his specimen. He replied that he hoped so — the nurse was doing the examination but she hadn't told him whether or not he passed.

I don't know who my grandfather was; I am much more concerned to know what his grandson will be. — Abraham Lincoln

Child Psychiatry

Behavior Problems and Cerebral Dysfunction in Children[*]

In the course of a day's work the physician in general practice will probably see three or four patients who would be designated "behavior problems." These may be minor in scale and intensity when compared to the caseload of a child guidance clinic. They are rarely minor to the parents and may actually be creating havoc in the household or schoolroom. It is a well recognized fact, however, that the nature and severity of the symptoms are no index as to the nature and severity of the problem behind them.

This report is concerned with the small number of such behavior problems which originate in the failure of the parents or teacher to recognize, understand and accept the fact that a subtle neurological handicap in the patient may be a contributing factor. It is often the physician's responsibility to evaluate such behavior problems, to diagnose the organic defect, if there be any, and to provide counsel that will increase the parents' understanding of their child, and hopefully thus relieve some of the attendant tensions in his home or school environment. It is these tensions, really, that bedevil him.

Silver[1] states, "The behavior of a child with brain damage is not only a function of the biologic damage itself, but it is also dependent upon the child's psychological defense patterns and upon the environmental forces acting upon him. The biologic defect in turn, however, influences the child's psychologic structure, its maturation, its gratifications, and defense patterns, so that we are in effect dealing with a reciprocal interaction of biological, psychological, and environmental forces, all of which need evaluation in understanding the child's behavior."

Experience has demonstrated that children with obvious neurological handicaps such as palsy, convulsions, severe retardation or degeneration rarely manifest the perplexing behavior problems with which this paper is primarily concerned. Bender[2] states, ". . . when a child with a recognized handicap becomes a problem of sufficient severity to come to the hospital, there has usually been some other more significant social or emotional factor than the specific handicap."

The cerebral dysfunction, which is the concern of this paper, is so minimal it escapes recognition. Too often, if unrecognized, it may become a significant factor in the genesis of behavior problems.

It is still a common misconception that occult cerebral dysfunction will cause abnormal behavior. It is often inferred that brain injury may result in objectionable behavior in the child and delinquent behavior in the adoles-

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[*] *Editor's Note:* Dr. A. S. Anderson, a pediatrician, has prepared a very interesting paper on a difficult and troublesome problem for most of us. It is presented in two parts. The first section defines and illustrates the problem. The second will deal with diagnostic procedures, treatment and prevention.

Continued

cent. The same concept provides basis for the idea that objectionable and delinquent behavior is possibly inevitable in certain instances of brain injury. Time and experience are proving this concept untrue. In my own practice I have made the following observations, which in my mind tend to refute the theory in question.

1. Severe head injuries resulting in permanent neurological sequelae without any permanent behavior problem.

2. Hitherto unrecognized stigmata of organic brain damage in children with ideal behavior.

3. The dramatic appearance of behavior problems when parents gain understanding and are enabled to accept the handicap of their brain-injured child.

4. The persistent post-brain infection or head-injury behavior problem limited to those children in whom such a problem would be expected even in health, because of emotional stresses within the family.

Concerning a series of 86 children with head injury behavior problems Bender[2] stated that in all but two who had posttraumatic epilepsy no one organic defect or any combination of them was the sole reason for the behavior disorder or personality maladjustment.

In a discussion of his own paper, Neurology and Psychiatry in Childhood Posttraumatic and Postencephalitic Syndromes, Blau[3] said, "Although I stated quite definitely in previous reports that there is a distinct posttraumatic and postencephalitic syndrome, I have learned differently. I am now trying to retract some of the things I wrote previously. As I studied these children more carefully and worked with the parents, the picture became more clearly psychiatric and one that should not be dismissed as an incurable organic condition."

The causes of cerebral dysfunction itself are really outside the scope of this paper, but because paranatal difficulties are so often cited by physicians and parents as significant in the etiology of behavior problems, I feel justified in pointing out here that the expensive, arduous, anticipatory longitudinal studies necessary to establish the organic factors in behavior problems are yet to be reported. Pasamanick[4] has done a large community epidemiological study in which it would appear that prematurity, toxemia and hypertensive disease of pregnancy are more significant in the origin of behavior problems than prolonged labors or difficult or operative deliveries. Keith, Norval and Hunt[5], at the Mayo Clinic, in a study which followed 4,464 children from one to seven years, found 1.3% had neurological lesions, but difficulties during delivery had little to do with the abnormalities in the infants who lived. No evidence was found that prolonged labor, asphyxia or delayed respiration caused any neurologic defect in the children who lived.

To demonstrate the genesis of the particular group of behavior problems which are the concern of this paper it will be helpful to consider six case reports, in brief. They have been selected because (1) they illustrate dysfunction in each of six areas of cerebral function and (2) they clearly demonstrate behavior problems whose cause is lack of recognition of the neurological functional handicap deriving from a subtle organic brain defect.

Case Reports

Neuromuscular Dysfunction

The only son of an ambitious executive was eight and one-half years old and in third grade. His problems were fearfulness, poor school achievement, failure to complete his classwork and an unusual number of minor ailments which required medical attention. The significant abnormalities found on physical examination were poor coordination, hyperactive knee jerks in the prone position, and allergic rhinitis. In order to develop "aggressiveness, courage and competitiveness" in this passive youngster the father had inaugurated a program of increasingly intensive athletic drills. Though under excellent executive management this program was failing to make either an aggressive athlete or courageous defender. By means of the examination and the interview following, the well-meaning father was helped to recognize his son's coordination handicap and the fact that the athletic drilling had not only frustrated but had also further incapacitated the boy. This insight opened the way to further insights regarding healthy parent-child relationships and their importance to emotional growth. As a result this boy's multiple symptoms, which were his reaction to pressure and misunderstanding, disappeared almost over night, though his coordination defect is still demonstrable.

This case study presents a defect in neuromuscular function which, until recognized by the father, contributed in part to a parent-child misunderstanding which in turn contributed to school, behavior and medical problems.

Intellect Dysfunction

This child was six and one-half years old when her mother consulted the physician. According to her mother, the child was chronically unhappy, subject to frequent severe illnesses, and achieving poorly at school. Hospital reports of the child's past illnesses, however, failed to confirm the mother's reports regarding their seriousness or severity. Physical examination revealed incoordination and hyperreflexia. At this point it was strongly suspected that the child was brain-injured and had handicaps in other areas as well. Psychological testing revealed an I.Q. of 80, but only minimal disturbance in the area of perception. An I.Q. of 80 is borderline for special class placement in school, but since she was not achieving in the regular classroom, she was placed in a special class. With relatively little interpretation the parents came to understand and accept the child's limitations, and consistently each time she has been seen during the past three years, the mother has reported her to be outgoing, happy, and no longer subject to frequent or severe illnesses.

This case demonstrates that recognition and understanding and acceptance of the child's neurological limits (especially in the area of intellect) created a new emotional environment for her, one in which she could be happy (despite her continuing handicap) and medically healthy.

Perception Dysfunction

An only child was brought to the physician at the age of nine because of his disturbing classroom behavior. The teachers had also observed problems in achievement, socialization and coordination. Physical examination revealed abnormalities in coordination and tendon reflexes. Psychological testing revealed an I.Q. of 93, accompanied by severe perceptual abnormalities. The electroencephalogram tracing was markedly abnormal. Conferences with parents and teachers proved ineffective. Rapport with the father was obviously unsatisfactory, and he overtly manifested this by becoming a chronic credit problem. Intensive trials of several drugs brought about no significant or permanent improvement in the patient's behavior. A psychiatric referral was not acceptable to the parents. Later, an opportunity to observe the child vacationing with several other children presented itself. In this setting he demonstrated no neuromuscular or socialization problems. The following year he was expelled from school because of unacceptable behavior. At this time the parents secured a tutor for him. She acquired keen insights into the boy's problems and was successful in her special teaching program. She developed excellent rapport with the parents and through her they themselves gained insight and understanding of their son's achievement and behavior problems. In retrospect the parents also give credit to the book, *The Other Child*, by Lewis, Strauss, and Lehtinen.[6] Lewis is a father who had a

Continued

child with a similar brain injury problem, and Strauss, a teacher by profession, has been a pioneer in the education of brain-injured children.

Several years have passed now since this boy's parents had their significant experience with his tutor. Though the boy continues to have school achievement problems, his behavior has not indicated need for further professional help. Incidentally, the parents' credit problem evaporated, and as they gained in understanding and acceptance of this child their need for constant pediatric help diminished.

This is obviously a complex problem, but for the sake of simplification we can say that some of the stress associated with school was basic to the child's social behavior, since in a vacation setting his behavior was relaxed and unobjectionable. Even his school behavior improved when his parents and teachers came to understand and accept his specific handicap.

Impulse Activity

A girl came to the physician as a seven-year-old child known to have severe neuromuscular and perceptual and impulse dysfunction. She had done well in a special school for children with perceptual handicap. The parents came for help in making plans for her to attend a boarding school. They were distressed in particular over her agitated, destructive behavior at home during and immediately following a period during which the parents were away on a vacation. During this holiday the woman who was staying with the girl brought her to the physician with symptoms of fever and respiratory disease. No infection was found. At this time the physician wasn't insightful enough to question the woman concerning the real problem, the child's behavior. The physician did record in the chart the observation that the child's temporary guardian demonstrated very little understanding of her and seemed inept in her management. Aside from making this note, the physician reassured the guardian the child was free of infectious disease.

To prevent rampant hyperkinetic behavior in obviously brain-injured children with excessive impulse activity there is a need for support in the form of kind, understanding, firm and consistent discipline, and protection from excessive emotional stimuli. Discipline and protection were obviously lacking while the parents were on vacation. When the mother gained insight into the situation the behavior problem disappeared. It was not necessary to place the child in a boarding school.

Neurosensory Defects

The patient in this case study is a seven-year-old girl known to the physician since she was age one. She has rarely needed pediatric attention, and as well as could be determined from the records, her family relationships should have been excellent. Her teacher, however, called the mother's attention to the fact she was out of contact in the classroom and was falling behind in reading. A correctable visual defect was discovered, and glasses seem permanently to have cured her behavior and learning problems.

Distortions in Sensorium

A ten-year-old girl had a chronic respiratory allergy problem. At the age of four years she had one grand-mal convulsion and following this paroxysms of unconsciousness. When she was ten years old her teacher noted that she was under-achieving in school and her behavior was characterized as "not being with it." A provisional diagnosis of petit-mal epilepsy was made and Tridione was added to the drug regimen. She responded dramatically; her school achievement and behavior problems disappeared and her need for pediatric visits was limited to those periodic checks of blood and urine necessary in Tridione therapy.

This case demonstrates the elimination of the behavior problem characterized as "not being with it" when specific therapy was introduced; when the patient's behavior returned to normal the minor medical problems disappeared.

In each of these six patients an abnormality in behavior was one of the major presenting symptoms. The specific problems were unwarranted fearfulness, generalized unhappiness, unacceptable school behavior, agitated, destructive activity, and daydreaming in the classroom. When the cerebral dysfunction in each case was recognized, understood and accepted by the adults in the child's environment the behavior problems disappeared. The problem of under-achievement in school was relieved in four cases and the need for an excessive number of pediatric visits was notably lessened in three. That the cerebral handicap was the result of an organic neurologic defect was confirmed by its persistence even after the creation of a different emotional environment at home and at school had made it possible for the child's offensive behavior to be resolved.

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Medical Schooling of the Past

It may be interesting to turn back the pages of history a few hundred years, to see what some of the really old boys had to study and stomach. Blasius Gronewalt began his medical schooling at the University of Leipzig in 1506 and in later years the books that he had used were collected by the library of Kreuzschule at Leipzig. There were only two medical books in the collection. One was the tractates and expositions of Petrus Hispanicus, who was a practising physician during the late thirteenth century, having studied at Montpellier and Paris. This book concerned treatment and dietetics and was based a great deal upon the sayings and teachings of Hippocrates (460-370 B.C.) and Galen (130-200 A.D.). The other medical book was the "Pandectae Medicinae" by Matthaeus Sylvaticas, which was a reference text of pathology and pharmacology. All of the other books were of a nonmedical nature and included texts on metaphysics, astrology, politics, ethics, economics, famous editions of Aristotle and the works of Cicero, Caesar, Plutarch, Valerius Maximus, Ovid, Livy, and Quintilian. In addition, the poor fellow had to study Greek!

— **F. William Saul, M.D.: Pink Pills for Pale People**

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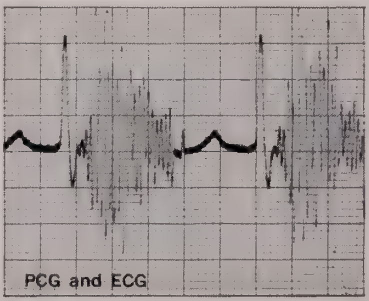

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Surgical Seminar

Lymphedema of the Upper Extremity

Presented as a seminar sponsored by members of the faculty of the Mayo Graduate School of Medicine.

LYMPHEDEMA WAS observed as long ago as 1500 B.C. in India where elephantiasis apparently occurred commonly enough to warrant marriage restrictions.[1] Hippocrates had experience with various swellings of the extremities and treated them by scarification. In spite of this early beginning, until recently not much has been known about the etiology, pathology, and pathogenesis of lymphedema. The work of Kinmonth and associates[2] with direct lymphangiography has provided some information on the etiology of the edematous limb by pinpointing some of the structural defects that exist in the lymphatic systems of these patients.

Basic Considerations

Definition of Terms

Lymphedema is the specific type of edema due to accumulation of lymph in the soft tissues. It has been defined[3] as the edema which results from lymphatic obstruction, has certain microscopic qualities, and differs clinically from venous edema.

Anatomy of the Lymph Vessels

The human integument has a rich lymphatic supply, consisting of a superficial and a deep capillary plexus. The superficial plexus forms a freely anastomosing network in the papillary layer of the skin; its vessels are composed of a single endothelial layer and have no valves. This layer is connected to a deeper layer between the dermis and the subcutaneous tissue. These latter channels are larger, may have smooth muscle in their walls, and have valves which give them a beaded appearance.

The lymphatic network of the hand consists of dorsal and palmar plexuses which converge and course up the volar surface of the forearm as ulnar and radial channels, ultimately terminating in the axillary lymph nodes.[4] A deeper system follows the large vessels of the arm and also empties into the axillary lymph nodes with or without intervention of the deep cubital lymph nodes. The superficial and deep systems are connected at the elbow.

A lateral channel, which courses with the cephalic vein in the deltopectoral groove before entering the subclavicular or supraclavicular lymph nodes, is an important collateral after radical mastectomy.

Physiology

The endothelium of the lymphatic vessels is more permeable than that of the blood capillaries. The main function of the lymphatic system is to return large molecules, such as proteins, to the blood. The passage of fluid from the blood capillaries to the tissues is described by Starling's hypothesis. Thus increased capillary hydrostatic pressure, decreased capillary osmotic pressure, and increased capillary permeability may cause edema.

The most important factors governing lymphatic flow are the movement of muscles and the competency of lymphatic valves. Webb and Starzl[5] pointed out that the pulsations of large arteries may be important. The circulation of lymph is rapid; Blocker and coworkers[6] have shown that circulation from the foot to the thoracic duct in humans in a

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supine position under general anesthesia requires about three minutes.

Lymph contains fibrinogen, prothrombin, lymphocytes, erythrocytes, urea, creatinine, sugar, chlorides, and amino acids. Kinmonth and Taylor,[7] in studying patients with congenital lymphedema of the legs, found that the protein content of the lymph was increased, the average being 2.5 gm./100 ml. (normal[8] for human skin lymph, 0.69 gm./ 100 ml.) and that the rate of absorption of lymph was considerably slower than in the normal extremity.

Regeneration of lymphatic vessels is rapid unless excess scar formation and infection supervene. Reichert[9] showed that regeneration begins as early as the fourth day and that by the eighth day regeneration of vessels across a scar is physiologically complete.

Pathogenesis

Regardless of the cause of lymphedema, a consistent sequence of events occurs. Stagnation of lymph in the vessels causes gradual dilatation, the valves becoming incompetent if the lymphedema persists long enough. The protein content of the tissues increases and, since lymph is an excellent medium for fibroblastic growth, fibrosis ensues which further increases lymphatic blockage. Infection is also likely to occur in this protein-rich transudate, with resultant thrombosis and blockage of lymphatic vessels.

Lymphedema may be clinically divided into inflammatory and noninflammatory types (Table).

Classification of Lymphedema*

- I. Noninflammatory
  - A. Primary
    - 1. Lymphedema praecox
    - 2. Congenital lymphedema
      - a. Hereditary or familial (Milroy's disease)
      - b. Simple
  - B. Secondary
    - 1. Malignant occlusion
    - 2. Surgical removal of lymph nodes
    - 3. Pressure
    - 4. Roentgen and radium therapy
- II. Inflammatory
  - A. Primary (single or recurrent acute and chronic)
  - B. Secondary (single or recurrent acute and chronic)
    - 1. Venous insufficiency
    - 2. Trichophytosis
    - 3. Systemic disease
    - 4. Filariasis
    - 5. Local tissue injury or inflammation

*Reproduced with permission from Allen, E. V., Barker, E. W., and Hines, E. A., Jr.: Peripheral Vascular Disease, Ed. 3, Philadelphia, W. B. Saunders Company. 1962, p. 695.

Etiology

Noninflammatory Primary Lymphedema

Primary noninflammatory or idiopathic lymphedema includes the congenital types (hereditary or simple) and lymphedema praecox.

Although involvement of the upper extremity by congenital lymphedema is very rare, cases have been reported.[10,11] In the simple type, one family member is involved; while in the hereditary type a number of blood relatives are affected. Clinically there is diffuse swelling involving part or all of the extremity but without pain or ulceration. The swelling, usually noted at birth, is firm but subsides greatly on elevation of the extremity. The cause is unknown, although heredity probably is a factor.

Lymphedema praecox usually develops during the first or second decade of life and is rare after 40 years of age. Swelling generally begins distally in the foot and slowly progresses proximally. Females predominate in a ratio of about 10:1.[12] In a recent study of 122 patients with lymphedema praecox, Schirger and associates[12] found that the upper extremities were involved in five patients and the genitalia in two.

The cause of lymphedema praecox is unknown. The predominant incidence in women, with onset during adolescence and worsening during menstruation, indicates that the reproductive system may be related to the problem.

Kinmonth and associates[13] studied 87 cases of idiopathic lymphedema (12 of 107 cases were congenital) by lymphangiography. Hypoplasia was found in 55% and aplasia in 14%, the latter occurring more frequently in the congenital and in the more severe cases. Dilated or varicose lymph channels were found in 24% and were also more frequent in the congenital group. A familial tendency and a 14% incidence of other associated congenital anomalies lend support to the theory of congenital lymphatic maldevelopment as a cause of idiopathic edema.

Pathologically, the changes in lymphedema praecox are similar to, although not as marked as, those in congenital lymphedema.[12] The subcutaneous tissues are thickened, and the skin is rough. Microscopically, dilated lymphatic spaces lined by endothelial cells and hyperkeratosis may be seen. The epidermis undulates and often atrophies over the edematous projections of dermis. Lymphedematous tissue of long duration generally shows fibrotic change, disruption of collagen fibers, and fragmentation of elastic fibers of the dermis with attenuation of superficial lymph vessels by perilymphatic inflammatory reaction, interstitial edema, and fibrosis.

Noninflammatory Secondary Lymphedema

This type of lymphedema may be caused by lymph nodal occlusion by lymphoma, surgical removal of lymph nodes, extrinsic pressure on lymph vessels, or roentgen or radium therapy. It is characterized by rather sudden onset of swelling and by more rapid progression than in idiopathic lymphedema. Lymphangiographic studies in these patients may reveal dilated or tortuous channels and accentuation of the subcutaneous pattern of small lymph vessels, known as dermal reflex. Kinmonth and associates[13] stated that the lymphatic vessels rarely show more than the smallest degree of dilatation in obstructive lymphedema but that the dermal backflow is always striking.

In many patients, lymphedema develops after radiation therapy subsequent to surgical ablation of lymph structures; whether the swelling is due to radiation fibrosis or to the surgical procedure is uncertain. Irradiation obliterates lymph sinuses and closes channels, but the beneficial effects of 50 to 80 r of x-radiation in acute obstructive lymphangitis or lymphadenitis cannot be denied. West[14] reported excellent results in treating postmastectomy lymphedema with doses of 100 r and stated that x-radiation relieved vascular spasm, permitting better drainage.

Whether cobalt-60 teletherapy will decrease postoperative lymphedema is currently unknown.

Lymphedema After Radical Mastectomy

The swelling of the arm that occurs after radical mastectomy is the most common type of lymphedema of the upper extremity. Unfortunately, the pain and disfiguration of the lymphedematous arm postoperatively may be as psychologically traumatic to the patient as the initial shock of the operation.

The reported incidences of lymphedema after radical mastectomy are extremely variable because of lack of standard measurements and because of differences in definition of what constitutes a swollen extremity. Some degree of swelling exists in approximately 50% of patients and is severe in five to 30%.

Stillwell[15] listed three types of swelling that occur following radical mastectomy: acute transient, transient acute painful, and persistent painless edemas developing at various intervals postoperatively. Theories of causation are numerous but are based primarily on venous or lymphatic obstruction.

INFECTION

Halsted[16] thought that lymphatic and venous obstruction contributed to postoperative swelling but that infection, often subclinical, was actually the cause of the swelling. Because infection led to axillary cicatrization which caused or accentuated the swelling, Halsted believed that reduction in axillary dead space was important in reducing the incidence of infection. The strongest argument in favor of skin grafting is that it reduces dead space. Villasor and Lewison[17] found no correlation between skin grafting and postmastectomy lymphedema but thought that infection was the most important single factor causing or increasing the lymphedema. Daland[18] stressed the importance of avoiding infection and emphasized that the skin incision for radical mastectomy should not be on the arm.

VENOUS OBSTRUCTION

Russo and co-workers[19] measured venous pressure and performed venography on 15 patients preoperatively and postoperatively; they demonstrated complete axillary vein

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block in five and moderate distortion of the venous lumen in six. They concluded that venous changes were due to extensive dissection around the axillary vein, causing phlebitis or thrombosis with subsequent increased venous pressure and stasis.

In 1960 Smedal and Evans[20] suggested that postmastectomy edema of the arm was due to thrombophlebitis of the axillary vein with concomitant inflammatory lymphatic obstruction in the perivascular sheath. They reported clinical evidence of thrombophlebitis in 85% of their cases and venographic evidence of phlebitis in a high percentage. Extensiveness of the surgical procedure and presence of axillary metastasis were the two most important predisposing factors to thrombophlebitis. If thrombophlebitis is the cause of postmastectomy lymphedema of the arm, the possibility of prophylactic anticoagulant treatment arises.

However, Schorr and associates[21] found no correlation between the state of the axillary vein, as seen on the venogram, and arm swelling; but on venography of 18 patients without arm swelling postoperatively, the cephalic vein was seen in 16. Thus, preservation of the cephalic vein may be important in preventing postmastectomy lymphedema. They commented on the difficulties in interpreting venograms, pointing out that axillary vein compression on the venogram may be physiologic due to clavicular compression of the vein as it enters the subclavian vein.

MacDonald and Osman[22] advocated axillary vein resection, with preservation of the cephalic vein, as part of the axillary dissection because it permitted more complete dissection and did not increase the incidence of postoperative swelling. They thought that arm swelling was due to lymphatic obstruction caused by perivenous lymphangitis, which was eliminated by resection of these channels when the axillary vein was resected.

OTHER FACTORS

Thrombophlebitis with resultant venous and arterial vasospasms has led to treatment of postmastectomy lymphedema by stellate ganglion block. However, the effect of vasospasm in the development of lymphedema is not clear.

There are many opinions concerning the role of irradiation in postmastectomy lymphedema. Some consider the development of radiodermatitis to be important, not the use of irradiation *per se*. In a large series of cases studied by statistical analysis, Treves[23] found that patients treated by x-ray, especially preoperatively, had a higher incidence of arm swelling. However, x-ray treatment alone was not associated with the higher incidence of swelling.

Obesity seems to be the only predisposing factor on which various authors agree. It is generally true that obese patients have a higher incidence of lymphedema, and their lymphedema is of greater severity. This is perhaps related to the fact that obese patients are more likely to have skin flap necrosis and secondary infection; it also may be explained by the necessity of removing more fatty tissue and, consequently, more lymphatic vessels.

Treves[23] summarized the possible causes for postmastectomy lymphedema as follows:

"It appears that lymphedema following radical mastectomy cannot be attributed to any solitary factor, but a combination of several factors may operate in any given case. Probably the most frequent cause is interference with the return of lymph because of ablation of the profunda lymphatics with the nodes of the axilla. Interference may be due directly to the axillary dissection or to cicatrization following infection or fibrosis following roentgen-ray therapy. Angulation of the vein, interfering with both venous return and return of lymph from vessels in the wall of the vein, and reflex spasm of the axillary vein must likewise be assessed as bearing directly on the problem."

Prophylactic measures to prevent lymphedema after radical mastectomy should include avoidance of infection and excess trauma to the axillary vein, sharp surgical dissection, weight reduction, and discriminate use of irradiation.

Inflammatory Lymphedema

This type is characterized by recurrent episodes of lymphangitis and cellulitis with chills, fever, and constitutional symptoms. When it occurs, the upper extremity becomes swollen, red, hot, and tender to the touch in a short time. Streptococci are usually responsible for the acute episodes, although staphylococci may be the cause. The regional lymph nodes are often swollen and tender, and the swelling may persist long after the signs of inflammation have subsided. If there is recrudescence, lymph channel thrombosis and fibrosis further obstruct the lymph vessels. The lymphedema may be primary or secondary to local injury, infection, or systemic disease.

Lymphangiosarcoma

Since Stewart and Treves'[24] report in 1948, 83 cases of lymphangiosarcoma, a rare malignant neoplasm seen most commonly in the lymphedematous arm after radical mastectomy, have been reported.[25] After an average cancer-free interval of eight years, purplish-red, subdermal, macular lesions arise on the arm or antecubital area; secondary satellite areas develop which may adjoin and continue to spread up the arm, and new lesions later appear on the adjacent part of the thorax. Neither the nature of the original neoplasm nor the recurrence of it seems to be a factor in this condition, for it has occurred after radical operation for benign breast diseases and has even been reported in chronic lymphedema of the lower extremities. Treatment consists of forequarter amputation with or without x-ray therapy or x-ray therapy alone; but death from pulmonary metastasis usually ensues shortly. For this reason, prophylaxis and treatment of lymphedema are imperative.

Treatment

Medical Treatment

It is as difficult to treat lymphedema as it is to prevent it, and many times the treatment is only palliative. It is important that, from the start, both physician and patient understand the chronicity of the swelling and realize that present measures aid only in controlling swelling but do not effect a cure. If possible, the patient should be hospitalized for a few days of bed rest so that the extremity can be elevated and as much edema fluid mobilized as possible. Diuretics taken orally may help but, except in very mild cases, will not control the swelling if used alone. Prophylactic administration of antibiotics should prevent recurrent cellulitis and lymphangitis. Babb and associates[26] noted excellent results in a small group of patients treated by prophylactic administration of penicillin. Local measures, such as careful hand care and avoidance of even minor trauma, are very important because even a trivial insult will cause decompensation when the lymphatic system is already in a precarious state.

The physiatric management, at the Mayo Clinic, of patients with postmastectomy lymphedema has been outlined by Stillwell[15] and is basically similar to the programs used at other institutions. The extremity is periodically elevated during the day and as much as possible during the evening. The physiatric program, given twice daily, consists of 60 to 90 minutes of treatment with a pneumatic pump followed by 10 minutes of manual massage; then instruction is given in the techniques of isometric exercises and bandaging. Gentle kneading and friction techniques of massage prove effective in increasing the lymph flow in the extremity. Opinions differ regarding the effectiveness of various pneumatic pumping devices, but Tinkham and Stillwell[27] concluded that, although a greater number of patients treated for three days or more obtained a 30% reduction of edema when a pneumatic pump was used, treatment not including such a device is worthwhile. Active muscular exercise is stressed because it increases the flow in lymph vessels and veins as a result of the muscular pumping action. Exercises are done as nearly isometrically as possible, with the arm bandaged.

The home-care program also consists of elevation of the extremity, elastic support, and isometric exercises; it should be adhered to in a rigidly systematized manner. The patient is told to avoid using the arm for household tasks for longer than 15 to 20 minutes at a time and to avoid local heat and hot environments which increase lymph and blood flow.

Continued

The most important single part of the treatment program is the use of adequate external elastic support. This provides tissue hydrostatic pressure and prevents transudation of fluids into tissue spaces. Early in the program, a double, three-inch, woven elastic bandage is used; later, a fitted sleeve of the Jobst type may be worn. The patient is told to wrap the arm before rising in the morning and to reapply the bandage several times during the day. Usually, six to 12 weeks are required for the arm to reach its minimal size and another two to three months for the connective tissue to shrink. The patient may then remove the bandage at various times at the end of the day and note the length of time before swelling returns. The time varies, but most patients can go for several hours daily without the elastic bandage.

Stillwell[28] pointed out that most patients have two chances in three of eliminating a third of their swelling in the first four or five days of treatment. After that, improvement is slow, and patients may do as well on the home-care program as they would in a physiotherapy section.

Schwartz[29] reported favorable results with the use of hyaluronidase by iontophoresis in the treatment of lymphedema in five patients. However, he also emphasized that elastic support is needed to prevent the swelling from recurring.

Surgical Treatment

Many surgical procedures, either physiologic or excisional, have been used for prevention or treatment of lymphedema.[30] The physiologic operations provide reestablishment of continuity of deep lymph vessels, prevent angulation of the axillary vein and interruption of the venous return, and obliterate the axillary dead space.[31] These include the Kondoleon operation, use of long silk or nylon sutures bridging the axilla, pedicle skin grafts around the area of lymphatic obstruction, and placement of absorbable gelatin rolls (Gelfoam) around the axillary vein and various muscles around the axilla to obliterate dead space and provide a lymphatic bridge. Although good results are still claimed with some of the surgical procedures, the great number and variety of procedures attests to their general ineffectiveness.

The excisional operations are done for severe and chronic cases of lymphedema, less commonly on the upper extremity. Indications for excisional treatment are increase in size of the extremity, significant impairment of function, repeated infection, unsightly appearance, emotional disturbances because of the deformity, and changes in the skin such as thickening, induration, and dermatitis.[32] Basically, the excisional operations consist of removing various amounts of skin and subcutaneous fascia down to the underlying muscle and closing the defect primarily or with a skin graft. These operations are not universally successful and leave much to be desired cosmetically; however, the incidence of recurrent lymphangitis and cellulitis is decreased postoperatively. The use of elastic support is again of paramount importance.

It is hoped that in the future a more physiologic method for the treatment of lymphedema will be found. Transplantation of lymphatic vessels and reconstruction of lymphatic channels may provide a new approach to the problem.

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A charitable man is like an apple tree — he gives his fruit and is silent; the philanthropist is like the hen.

Clinical Path Conference

Childbirth and Sudden Death

A thirty-nine-year-old mother of eight children entered the St. Barnabas Hospital on the afternoon of September 26, 1964, in early labor. Except for the discomfort of severe varicose veins of the legs and the vulva, her pregnancy had been uneventful. She had gained 15 pounds. She had been observed by an obstetrician for the last seven months of her pregnancy. Her predicted date of delivery was September 21, 1964. Her hemoglobin on August 20 was 10.8 gm.% and on admission was 12.8 gm.%.

On admission the patient's blood pressure was 124/70. Her pulse and temperature were normal. The fetal head was high, and the cervix was not dilated. The fetal heart rate was 126. Between 1:00 and 2:00 p.m. the patient's membranes ruptured spontaneously. The amniotic fluid was stained with meconium. At 5:00 p.m. she became nauseated and vomited, but otherwise looked well. At 7:15 p.m. she complained of mild abdominal pain and then suddenly gasped and became cyanotic. No blood pressure or pulse could be obtained. She appeared to have swallowed her tongue. An anesthesiologist was called and administered oxygen. The patient's color return, but not the vital signs. Her cervix was fully dilated. She was taken to the delivery room where a viable infant was delivered by low forceps extraction at 7:45 p.m. The infant, a girl weighing nine pounds and seven ounces, was covered with deeply stained meconium. With the delivery of the head, 500 ml. of blood gushed forth. Following the expression of the placenta and massage of the uterus the patient lost about 200 ml. more of blood. While the delivery was taking place, she remained cyanotic without vital signs. She was given intravenous fluids, adrenalin, blood transfusions, Solu-cortef, and external cardiac massage; but she did not respond and was pronounced dead at 8:55 p.m.

Dr. Richard Reece

Dr. Mitchell, this was your patient. Have you anything to add to the history?

Dr. Mancel Mitchell

I was sitting at a desk across the hall from the labor room when this patient gave a gasp and became cyanotic. I came immediately and found her unconscious, with rigid, flexed upper extremities. A convulsion from toxemia was my first impression. She had a peculiar cyanosis in the upper half of her body. The anesthesiologist was in the hospital at the time, and the patient was given oxygen almost immediately. Her cervix was found to be fully dilated at this time with the presenting part on the perineum. An elective low-forceps extraction was done without delay. The baby was alive but died the next day. About 30 minutes elapsed between the mother's symptoms of dyspnea and shock and the delivery.

OB-GYN Resident: What was the blood pressure of the patient when she started vomiting?

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Dr. Mitchell: No record of the blood pressure was recorded at that time.
Dr. Reece: Was there tenderness along the varicose veins?
Dr. Mitchell: No, none.

Dr. Richard Fliehr

What happened to the fetal heart tones when she had her first episode? Were they heard at the time or was there so much mass confusion that they were not then noted?

Dr. Mitchell

At approximately 5:10, when she was nauseated, the fetal heart was recorded at 162/minute. Shortly after this episode, the heart beats were recorded at 130/minute. There is no further record.

Dr. Fliehr

Was there any demonstrable blood loss after the bag of waters ruptured, or before the delivery?
Dr. Mitchell: No.
Intern: When the patient became cyanotic and the cervix was dilated, was the head engaged or was it floating?
Dr. Mitchell: When she arrived at the delivery room, the baby's head was on the perineum.
Dr. Fliehr: Was any mention made of the consistency of the uterus at any time?
Dr. Mitchell: No.

Differential Diagnosis

Dr. Fliehr: Now let's consider the diagnostic possibilities in order of probability. Does the audience have any suggestions?

Resident: Abruptio placenta with embolus.
Dr. Fliehr: What kind of embolism?
Intern: Amniotic fluid.
Dr. Fliehr: What other possibilities are there?

Dr. Reece: With the varicose veins, sudden gasping for breath and shock, pulmonary embolism from the legs must be considered.

Dr. Fliehr: A thromboembolic phenomenon is a possibility, but it is more likely to occur after delivery. What other kind of embolism is possible?

Resident: An air embolus.

Dr. Fliehr

Certainly any of these embolic phenomena — amniotic fluid, thromboembolism, or air — could have led to sudden death in a young, pregnant woman. But emboli are not the only causes of death. Let's consider other areas.
Resident: Uterine rupture was my first thought.

Dr. Fliehr

Uterine rupture is certainly a possibility, especially in this patient who complained of abdominal pains before death. However, it is unusual for a rupture to occur this late in labor, and it is unusual to deliver from below with a uterine rupture. With only a partial rupture, however, a baby can be delivered vaginally. The patient's bleeding brings another condition to mind.

Resident: Cervical tear.

Dr. Fliehr: Yes, but with a cervical tear, the bleeding is usually external. There is another possibility which bears no relation to the uterus. It happened to us once.

Dr. John Popowich: Cerebral aneurysm.

Dr. Fliehr

Yes, cerebral aneurysm, cerebral hemorrhage, or even an unsuspected brain tumor. But of all the possibilities mentioned, the most logical is an amniotic fluid embolism following a massive premature separation of the placenta or abruptio. Let's have the pathologist relate his observations. My diagnosis is abruptio placenta with amniotic fluid embolism.

Pathological Discussion

Dr. Reece

The body was very cyanotic around the upper extremities and face. There were large varicosities of the right leg and also the right vulva. Upon opening the abdomen, we found about 500 cc. of blood in the mesentery posterior to the descending colon. In this hemorrhagic defect we noticed some greenish particulate matter. The uterus itself weighed 1600 grams, and along the left lateral side, a 15-cm. tear stretched from the cervix to the round ligament. This was not at the point of attachment of the placenta. Otherwise, the abdomen disclosed no real lesions. In the inferior vena cava we found more particles of green material. The spleen was enlarged and weighed 350 grams.

The chest cavity disclosed a normal heart, with no arteriosclerosis in the coronaries. The heart was filled with unclotted blood, and after two hours, this blood still did not clot. The lungs were normal in weight at 350 and 300 grams, and showed focal edema and atelectasis in the posterior segments. There were no pulmonary emboli: no blood clots in the pulmonary arteries.

Microscopically, the lungs demonstrated numerous vessels and capillaries filled with keratin and squamous epithelial cells. In one vessel, a lanugo hair was identified. These observations, of course, confirm the presence of amniotic fluid emboli. There was no infarction of the lungs, but scattered patches of edema were observed. Other organs had a normal microscopic appearance.

Dr. Fliehr: Did anyone check the placenta to see if there was evidence of premature separation?

Dr. Mitchell: Yes, we checked it, but saw no evidence of separation.

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Dr. Fliehr

The most common cause of rupture of the uterus is, of course, previous cesarean section, and, if it was a classical section, the rupture usually occurs before the onset of labor. This is not an absolute rule but a generalization. If it was a low cervical section, the rupture is more likely to occur during labor or at the time of delivery. I assume this girl had no previous cesarean sections. The other possibility is that during her gynecological career, she had a vigorous D and C with weakening of the uterine wall. This is often suspected but seldom proven. We had a patient with massive rupture of the uterus, who had a D and C three to four months before she became pregnant. That was the only plausible bit of history we could conceive of that could account for the rupture.

Certainly multiparity with an overdilated, overstretched uterus containing a large baby can lead to a weakened musculature of the uterine wall and possible rupture. I don't suppose the actual cause of the rupture is known in this patient. I am sure that many conjectures have been made, but I doubt if any final opinion has been arrived at. Is that right, Dr. Mitchell? Why should she rupture her uterus without any previous section or history of trauma?

Dr. Mitchell: We don't know.

General Comments

Dr. Fliehr

The phenomenon that actually caused death, the amniotic fluid embolism, usually occurs in elderly multigravida, with large babies and prolonged labor. Two of the facets are present here: she was an elderly multigravida and she did have a large baby; but she did not have a prolonged labor.

Emboli to the lung usually occur during or immediately after the delivery; it is unusual for them to occur before delivery. When the duration of labor is short, the predominant symptoms are pulmonary distress, shock, and death; and when prolonged, hemorrhage is a complicating factor with hypofibrinogenemia as an underlying cause. Atwood and Park, who examined the histological material from 220 parturient women,[1] found emboli from the trophoblast itself in over half of these women. The more sections they made of the lungs and the more special staining processes they used, the higher the incidence of the trophoblastic tissue found. They therefore concluded that almost all pregnancies have some trophoblastic emboli to the lungs.

In those patients in which emboli produce death, they attribute the excessive embolic material to "placental commotion," which can mean prolonged labor, uterine manipulation, or excessive contractions in eclampsia. Other factors such as placental infarction with a loosening of the trophoblastic tissue or its attachment to the villae could be contributory. In this case, the "placental commotion" was the rupture of the uterus, with probable placental infarction as well.

It is probably solid emboli rather than the systemic effects of amniotic fluid that cause the damage. Three men at the University of Sidney, Australia, injected amniotic fluid intravenously into two groups of sheep.[2] In one they filtered the amniotic fluid, and in the other they did not. In the filtered group, very little symptomatology was observed; whereas in the sheep given unfiltered amniotic fluid, the classical emboli phenomena were observed. This supported the concept of the Scots that solid emboli, not fluid, caused death. The incidence of amniotic fluid embolism is not high, but it is significant. At the Sloan Hospital for Women it is still the most common cause of maternal death during labor, delivery, and the immediate post-partum period.[3]

No effective treatment exists, especially in the massive case, as the patient is dead before heroic measures can be instituted. Oxygen by positive pressure is indicated. Some authorities advocate giving Papavarine hydrochloride for the reflex vasospasm. Atropine-like agents may be given for the cardiac depressive effects. Of prime concern, of course, is the treatment of shock with fluids, blood, and vasopressors, though with this injury to the lung already present, there is danger of promoting pulmonary edema, by the administration of excessive fluid.

If the amniotic fluid embolus occurs before the bag of waters is ruptured, amniotomy can be done to relieve intrauterine pressure, because increased uterine pressure may be the causative factor in pushing the emboli into the vascular system and thus into the lung. In almost all instances of amniotic fluid embolism the maternal fatality rate is extremely high. If the patients survive, it is usually pure chance.

While we are on this subject of embolism, let us consider air embolism. Criminal abortion accounts for the bulk of air embolism deaths; but if we exclude criminal abortion, air embolism can also occur at almost any time during delivery and the immediate post-partum period. There have been some recorded cases, for example, of it occurring in women who are put in a knee-chest position following delivery and during the post-partum period. Placental fragments can be dislodged in the knee-chest position, thus opening up the sinuses. Air can enter the uterus under negative pressure, enter the blood stream, and lead to fatal air embolism. There has been one reported case of a woman who merely flopped over in bed at night and from rolling over and lifting her leg, air entered into the vagina and the uterus with an air embolism. It can also occur by excessive manipulation of the uterus, especially following the expulsion of the placenta. This is one reason nurses should be instructed to be gentle with uterine massage.

In this particular case, without knowing the diagnosis, you might suspect premature separation of the placenta, because there is the same symptomatology as in the rupture of the uterus. There can be sudden abdominal pain with or without bleeding. Bleeding may be external or internal with dissection into the uterine tissue: a Couvalaire uterus. This gives abdominal pain. In the case of this unfortunate patient, a triple insult — amniotic embolus, rupture of the uterus, and hemorrhage — caused her death.

Dr. Mitchell

The latest report in the literature is from the University of Alabama Medical Center.[4] They list four additional cases and review symptoms, treatment, and pathogenesis. They also mention numerous therapeutic measures but emphasize the general ineffectiveness of treatment.

My original or provisional diagnosis as indicated on the chart was an

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acute abruptio placenta with amniotic fluid emboli. I also included a possible embolus from the infected thrombus from one of her varicose veins and a ruptured intercerebral aneurysm. I was surprised to learn of the ruptured uterus; but when I review the clinical story, I realize I should have thought of it first. The patient was a multipara with a large baby — both predisposing factors in rupture — but the lack of tumultuous labor and the lack of history of previous sections were against rupture. In the cases which were reported by the Minnesota Mortality Committee, half of them received oxytocin. This lady did not receive any oxytocin at any time, until after the placenta was delivered.

As we review this story now, rupture of the uterus is the most logical explanation and is something we have to consider with amniotic embolus. The incidence of death from amniotic fluid embolus varies from one in every 8,000 to one in 37,500 deliveries.[5,6] In Minnesota in a 20-year period, ten cases have been documented.

Dr. Reece

I would like to add something about the incidence. In Ontario from 1958 to 1960, 469,000 deliveries were studied.[7] In this group of patients 280 died: five of amniotic fluid embolus — an incidence of one in every 93,800 deliveries. Pulmonary embolism accounted for 14 out of 280 and air embolism for 12 out of 280: both more frequent than amniotic fluid embolism. As for the causes of maternal death among the 280 women, hemorrhage accounted for 33%, toxemia 12%, infection 23%, vascular accidents (including all types of emboli) 16%, anesthesia 7%, and miscellaneous 9%.

There are more than 100 reported cases of amniotic fluid embolism in the literature — 14 of which were nonfatal. The diagnosis of amniotic fluid embolism is one of exclusion. The only way to conclusively demonstrate it is to show amniotic fluid elements in the right heart; but it should be suspected in a patient who goes into sudden shock and shows the clinical or x-ray picture of pulmonary edema. Rupture of the uterus is a well known factor in producing amniotic fluid emboli.[8,9] The emboli, rich in thromboplastin, lead to widespread defibrination of the maternal blood, and consequent hemorrhage. In the Ontario study, 79 of the 280 maternal deaths were attributed to hemorrhage. Of the deaths from hemorrhage, 31 were the result of uterine rupture.

Anatomical Diagnosis

Spontaneous rupture of uterus with hemorrhage
Amniotic fluid emboli
Possible hypofibrinogenemia

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Grand Rounds

The Treatment of Multiple Sclerosis with ACTH*

Multiple sclerosis, by definition, is a demyelinating disease of the central nervous system, characterized by diffuse neurological deficits and an unpredictable clinical course marked by remissions and exacerbations. The etiology is unknown, and there is no known cure. Many different forms of therapy, ranging from Vitamin B_{12} injections to the intrathecal administration of tuberculin, have been tried and, for the most part, abandoned as ineffective.[1] The use of adrenocorticotrophic hormone (corticotrophin, ACTH) has, however, achieved relatively wide acceptance as the best method available at the present time for the treatment of multiple sclerosis. The status of this form of therapy is the main topic of this presentation.

Short Term Therapy Without Control Studies

The use of ACTH in the treatment of multiple sclerosis was first undertaken by Jonsson et al.[2] in 1949. Using initial doses of 25 mg., followed by 5 mg. every three hours to a total dosage of 300 mg. of ACTH, they reported improvement in two new cases but none in chronic cases.

In 1952, Fog[3] reported 20 cases and claimed improvement in 15 of them. Little attempt was made by him to categorize his patients according to age, sex, duration of disease, etc., and he did not employ any controls.

Merritt and Glaser[4] in 1952 reported a series of 33 patients treated with ACTH, none of whom had had remissions for at least three years prior to treatment. They reported significant improvement in 12 (36%) of their patients and either no change or mild alterations in the remainder. The effects were all transient, with a tendency towards relapse after discontinuation of the drug. In addition, these authors determined cerebrospinal

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*Presented as a Medical Grand Rounds at Mt. Sinai Hospital, Minneapolis, May 18, 1965.

Continued

fluid protein on all their patients before and after treatment and found no significant changes (Table 1).

TABLE 1
Effects of Corticotropin and Cortisone on Specific Symptom Complexes in Thirty-Three Cases of Multiple Sclerosis

Symptom Complex	Total No. Patients with Syndrome	Improvement Rating				
		1—	0	1+	2+	3+
Spastic-paretic	28	0	5	10	12	1
Cerebellar	24	2	4	11	6	1
Bladder	21	0	2	6	9	4
Sensory	23	0	20	3	0	0
Visual						
Chronic	11	0	10	1	0	0
Acute	3	0	0	0	2	1
Ocular movement	23	0	19	3	1	0

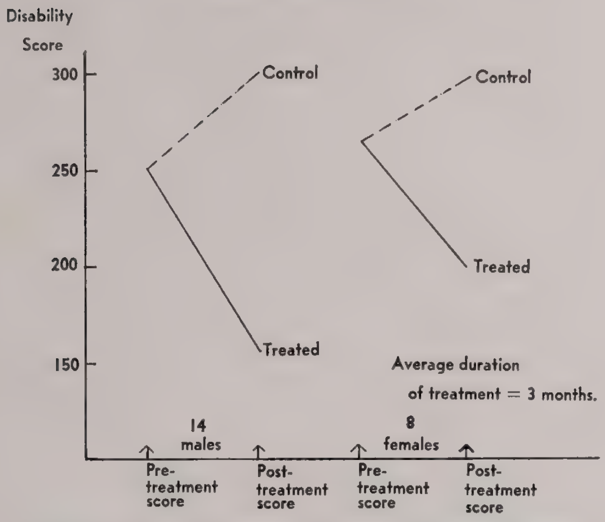
1— = slightly worse, 0 = no change, 1+ = slight improvement, 2+ = moderate improvement, and 3+ = pronounced improvement.
From Glaser, G. H., and Merritt, H. H.: Effects of Corticotropin (ACTH) and Cortisone on Disorders of the Nervous System. JAMA 148:898, 1952.

A similar study was reported by Rowland and Randt[5] in 1953, employing nine patients. These investigators found no improvement in any of their cases. In none of the aforementioned studies were control groups used. Merritt and Glaser used their treated patients as their own controls, but this was as close as anyone came to controlling his experiments. A second difficulty is encountered in attempting to interpret the extent of the patients' clinical response for purposes of comparing the results of one series with another, since there appears to be little uniformity between the various investigators' criteria.

Controlled Studies

Alexander, Berkeley and Alexander[6] in 1958 observed 554 patients for a total of 1,412 patient years, studying the natural course of the disease and its response to various forms of treatment. They used a scoring system devised earlier by Alexander[7] which consisted of assigning various numbers of points to different neurological signs and symptoms with a scale ranging from 0 (no neurological deficit) to 500 (completely bedridden and helpless). The progression and regression of the score was representative of the course of the disease when compared to the patient's subjective report, his ability to perform tasks, the social worker's report and the impression of the clinical examination. It also appeared reliable, with a correlation coefficient of 0.95 between scores obtained by six different examiners. Using this system they obtained data quantitating the course of the disease with correlations between numbers of exacerbations, their duration, severity, acuteness of onset and the level of disability before and after the attacks. They then selected 22 patients for treatment with ACTH and compared them with 22 control patients matched by age, sex, duration of illness and disability score at the time of initiating treatment and over the preceding three to 12 months. The average interval of treatment was three months, and the result obtained was an average reduction in disability score of 80 in the treatment group. This change was felt by the authors to be statistically significant (Figure 1).

FIGURE I
*Average Change in Disability Score in Patients Treated with ACTH



*Adapted from Alexander, L., Berkeley, A. W., and Alexander, A. M.: Prognosis and Treatment of Multiple Sclerosis — Quantitative Nosometric Study. JAMA 166:1943, 1958.

ACTH Regime

By 1963, Alexander et al.[8] had treated 110 cases of multiple sclerosis and again reported their experience. Using control and treatment groups as before, they tested patients on four different regimens:

1. High dosage ACTH for three months.
2. High dosage ACTH plus maintenance treatment.
3. Low dosage ACTH for three months.
4. Low dosage ACTH for one to four years (average 24 months).

They then grouped these patients into grading categories based upon the percentage reduction in the average pretreatment score. Grade A included all patients with a reduction in disability score of 40% or more; Grade B, all patients with a 25% to 39% reduction in score; and Grade C, all patients with a 10% to 24% reduction in disability score. Their results (Table 2) in general show significant response in Groups 1 and 2, with marked diminution in response in Groups 3 and 4. The questions of dosage and maintenance treatment will be considered later in this paper.

Prednisolone & Acetylsalicylic Acid Regime

In 1961 Miller, Newell and Ridley[9] conducted a study in which they attempted to evaluate the effects of prednisolone and acetylsalicylic acid on multiple sclerosis. Their 86 patients were randomly allocated to control and treatment groups, which were then compared and found equal for the following characteristics: sex, age, duration of disease and recent course (slowly progressive, fluctuant, rapidly progressive). The patients were evaluated on the basis of the Alexander score, the number of acute exacerbations, the number of new symptoms and signs appearing during the trial, and the patients' own subjective assessment 18 months after the institution of treatment. All patients were evaluated before and during

Continued

treatment by the same examiner, who was unaware of the treatment group to which any given patient belonged. Prednisolone was found to have no effect on the course of the disease, and the effect of acetylsalicylic acid was inconclusive.

However, in a study reported later the same year, the same authors[10] found more significant results for ACTH. They chose, out of a total of 120 referred patients, 40 who had unequivocal multiple sclerosis with new symptoms or signs of less than 14 days' duration, with no evidence of spontaneous improvement. These patients were divided into two groups (treatment and control) which were comparable as to age, presence of acute exacerbation and significant acute deterioration. The treatment group contained relatively more patients who were experiencing the initial episode of their disease (six compared to two for the control group). Patients in the treatment group received a three-week course of therapy consisting of 60 units ACTH gel intramuscularly twice daily for the first week, 40 units twice daily for the second week, and 60, 40 and 20 units daily on the second, fourth and sixth days respectively of the third week. The control patients received intramuscular injections of normal saline following the same schedule. In evaluating the results it was found that changes due to exacerbation represented too small a fraction of the total disability to use the Alexander scores, so the evaluation was necessarily subjective, using three categories. The authors pointed out, however, that the same examiner had evaluated all the patients and that he was unaware of the group to which each patient belonged. The three categories used were *Category A*, including all patients showing significant improvement within a few days, with their exacerbation entirely or almost entirely cleared by three weeks; *Category C*, including all patients showing no significant

TABLE 2

Effect of ACTH Therapy in Patients with Multiple Sclerosis Compared with Untreated Controls*

Group	N	Grade A (Reduction in Disability Score by 40% or More) % of N	Grade B (Reduction in Disability Score by 25% to 39%) % of N	Grade C (Reduction in Disability Score by 10% to 24%) % of N	No Improvement % of N
Control Group	18	0	11	19	70
ACTH (high dosage) after first 3 months of treatment					
Series I	18	22	39	22	17
Series II	21	29	33	19	19
Series III	55	31	33	20	16
Total	94	29	34	20	17
Subgroup (high dosage followed by maintenance treatment) after 1-6 years averaging 26 months:	37	41	21	19	19
ACTH (low dosage) after first 3 months:	16	6	13	37	44
Low dosage maint., 1-4 yrs., average 24 months:	12	8	0	25	67

*From Alexander, L., and Cass, L. J.: The Present Status of ACTH Therapy in Multiple Sclerosis. Ann Intern Med 58:454, 1963.

improvement after three weeks; and *Category B,* including those patients who did not fit clearly into either A or C. It was found that of the 22 treated patients, 11 were in Category A, eight in Category B and three in Category C. Results for the control group (18 patients) showed four in Category A, seven in Category B and seven in Category C. These results were felt to be statistically significant, even though the method necessary for evaluating the patients' responses was somewhat suspect.

Dosage

The dosages of ACTH employed by various investigators have varied considerably. Jonsson et al.[2] used initial doses of 25 mg. of Cortrophin (Organon) and subsequent doses of 5 mg. up to a total dose of 300 mg. Fog[3] used between 40 and 50 mg. of Acton preparations (Frederiksberg kemiske fabrikker) but did not have any well planned schedule of dosage set up. Glaser and Merritt[4] employed ACTH (Armour) in doses of 80-100 mg. per day for periods of five days to two weeks. The later studies used dosages expressed in terms of International Units of ACTH; one I.U. equals the biological activity of 1 mg. of international standard as determined by the adrenal ascorbic acid depletion method,[11] giving a more uniform dosage than before. The dosages used by Miller et al.[10] have already been mentioned. Alexander et al.[8] used two different dosage schedules, high and low, in addition to keeping some patients on maintenance doses for periods of up to six years. Patients on high dosage received 40 units of ACTH intravenously per day (or equivalent dosage of 60 units ACTH gel I.M. every 12 hours) for the first 10 days. They were then given 60 units of ACTH gel I.M. twice daily for 10 days, followed by gradual reduction of the daily dose by 20 units every three to five days until a maintenance dosage of 40 units daily was reached on approximately the 32nd day of treatment. This dose was then reduced variably until most patients were receiving not less than 20 units of gel three times a week. The low dosage regimen was identical with the maintenance phase of the high dosage regimen, i.e., 40 units of gel per day. The results (Table 2) were best for the high dosage regimen, especially when maintenance therapy was added.

Maintenance Therapy

Long-term maintenance therapy has apparently received serious attention in only a few centers. Alexander[10] has used it for as long as six years without apparent ill effect. Paulley[12,13] has used up to 40 units per day for several years without apparent ill effect and with supposedly successful prevention of exacerbations. However, his communications (in the form of letters to the British Medical Journal) do not seem detailed enough to draw any more than very tentative conclusions. Miller[1] maintains some of his patients on variable dosages for periods of three to six months but has a cautious attitude towards more long-term "prophylactic" treatment. At present there is little agreement on this subject.

Side Effects

In most of the series reported there was very little mention made of the side effects of ACTH, although they are generally felt to be less common

Continued

and less severe than those of corticosteroids.[1] The only authors found who dealt with them in any detail were Alexander and Cass.[8] They studied 12 of their patients receiving high doses of ACTH and divided the side effects into three groups, summarized below:

Group A (Onset on treatment days 5-24, average 12):

1. Superficial emotional excitement — 5 patients (1 equivocal)
2. Subjective G.I. symptoms — 3 patients
3. Tachycardia — 1 patient

Group B (Onset on treatment days 9-40, average 25):

1. Edema — 6 patients
2. Acne — 4 patients
3. G.I. bleeding (Guaiac positive) — 2 patients
4. Leukocytosis — 3 patients (16,200 to 20,400)
5. Infection — 4 patients
6. Mucous colitis — 1 patient
7. Pathologic fractures — 2 patients
8. ECG changes — 2 patients (1 equivocal)
9. Albuminuria — 1 patient

Group C (Onset on treatment days 21-60, average 34):

1. Hypotension — 3 patients (108/80 to 50/?)
2. Vertigo, syncope, dimness of vision — 4 patients
3. Hypoglycemia — 1 patient (FBS 75 mg%)
4. Hyperglycemia — 4 patients (120 mg% to 350 mg%)
5. Electrolyte changes — 4 patients:
    a. K increased
    b. CO_2 increased, Cl, Na decreased
    c. CO_2 increased, Cl, Ca decreased
    d. Na, Cl, Ca decreased
6. Mental changes — 8 patients (major psychoses in 4 patients)
7. Melanoderma — 1 patient
8. Death — 1 patient

Group A side effects were considered to be due to stimulatory effects of ACTH, Group B side effects to tissue changes, and Group C side effects to adrenal exhaustion. These side effects were correlated with the excretion of urinary 17-ketosteroids and 17-hydroxycorticoids which formed a curve showing three peaks and three troughs during the first sixty days of treatment on the average. The average onset of Group A side effects occurred at the height of the first peak (average day 12), Group B near the depth of the second trough (average day 26), and Group C near the onset of the third trough (average day 35).

Conclusions

Most of the available reports on the treatment of multiple sclerosis with ACTH are, at present, scant and mostly equivocal. For the most part they are uncontrolled, and there has been little attempt to standardize criteria for evaluation of clinical response, although this is very difficult. The most well controlled studies, however, support the value of ACTH treatment in acute exacerbations of the disease. There is even less evidence available on long-term maintenance therapy than on the use of ACTH for acute exacerbations; so the question of maintenance therapy is entirely an open one. The incidence of side effects is not discussed much, but it appears to be very low. However, the possibility of adrenal insufficiency during ACTH therapy apparently exists and should be watched for.

Case Report

A 53-year-old white female was admitted to Mount Sinai Hospital on March 3, 1965, with chief complaints of difficulty swallowing, stiff neck, lump in the left side of the neck and ease of fatigability. The history of her present illness dates back approximately three years prior to admission, at which time she noted onset of dysphonia and hearing loss in the left ear. She was seen at the University of Minnesota at that time, where paralysis of the left vocal cord and nerve deafness of the left ear were noted. Since then she had been noticing dysphagia for foods and easy fatigability.

Pertinent past history includes hypertension diagnosed eight years ago, and hypothyroidism diagnosed seven years ago. At admission, she was taking antihypertensive medications and grains three of thyroid daily. She was suspected at one time of having myasthenia gravis, but extensive workup failed to establish that diagnosis. General physical examination was negative except for a localized spasm of the left sternocleidomastoid muscle and paralysis of the left vocal cord. Neurological examination revealed a diminished right corneal reflex, a marked left N.VIII deficit, and hyperreflexia of the left triceps reflex. There was a questionable Hoffmann sign on the right and some dysmetria on the left.

Laboratory data including urinalysis, CBC, serum Na, K, proteins (total and A/G ratio), Ca, P and cholesterol were within normal limits. CSF examination revealed a glucose of 65 mg%, chlorides 602 mg%, protein 29 mg%, and negative VDRL, Wasserman and colloidal gold determinations. A muscle biopsy to exclude polyarteritis nodosa was negative. A consulting neurologist favored the diagnosis of multiple sclerosis and suggested a trial of ACTH therapy. Accordingly, the patient was placed on 25 units of ACTH intravenously per day for 14 days. There was no objective or subjective response to therapy and the patient was discharged on March 25, 1965.

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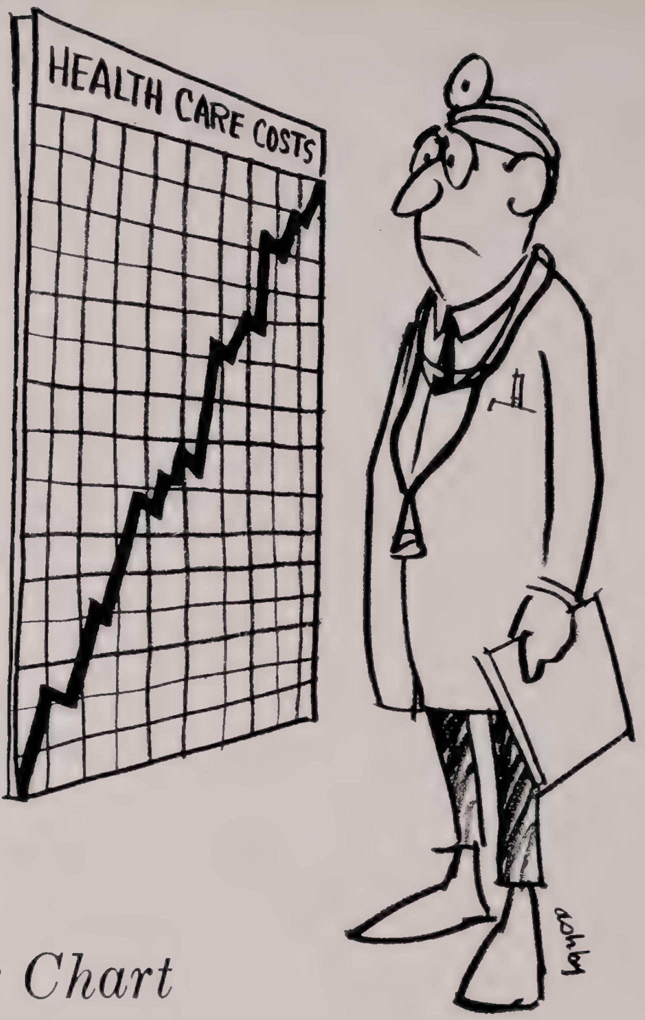
The only difference between a rut and a grave is their dimensions. — Ellen Glasgow



Fever Chart

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*Mechanism and Management of Intravascular Thrombosis**

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INTRAVASCULAR THROMBOSIS with its complications continues to be a problem for physicians in all types of practice. To date the understanding of the mechanism of thrombosis remains incomplete; however, certain factors appear to play some role in its causation, and an understanding of these is important in developing a therapeutic approach to the problem.

Consideration of the number of clinical situations in which thrombosis occurs suggests that multiple mechanisms of thrombosis exist. More than 100 years ago Virchow[1] proposed that three factors were important in intravascular thrombosis: (1) changes in the blood vessel, (2) stasis or slowing of the blood flow, and (3) altered blood coagulability. Despite the efforts of many investigators since Virchow, the relative importance and interplay of these factors in thromboembolism are still not clearly understood.

Blood Vessel Damage

The causative role of vessel damage in the formation of a thrombus seems plausible in inflammatory vascular diseases, degenerative arterial disease, and surgery or trauma, particularly of the blood vessels themselves. The mechanism of thrombosis secondary to vessel damage may be related to changes in electrical potential. Normally the endothelial surface of a blood vessel is electrically negative with respect to its wall, but the negative charge is lost with injury.[2] Experimentally it has been shown that thrombosis can be readily induced when a positive electrical potential is applied to a vessel wall; but if the potential is negative, it is almost impossible to induce thrombosis in the vessel.[3] The normal negative charge of the endothelium would tend to repel the platelets, which are also negatively charged.

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†Section of Clinical Pathology, Mayo Clinic and Mayo Foundation.

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Platelets

The probability that a mechanism involving platelets is operative in certain thrombotic disorders has considerable experimental and clinical support. The sequence of events which follows trauma to the endothelium of a vein has been studied by Wright.[4] Initially there is a deposition of platelets at the site of injury, followed by fusion of the platelets to form a plaque. The plaque enlarges and finally obstructs the blood flow, and ultimately the stagnant column of blood becomes clotted. Further evidence that platelets may be involved in thrombotic mechanisms is their content of phospholipids, which will accelerate clotting in vitro.[5] In addition, platelets have the property of adhesiveness, which is increased in the postoperative and post-traumatic states,[6] in both of which there is an increased incidence of thromboembolism. An increase in the number of platelets may be conducive to thrombosis, for conditions in which thrombocytosis occurs, such as polycythemia vera and the postoperative period after splenectomy, are not infrequently complicated by thrombosis.

Stasis

The importance of stasis in the formation of intravascular thrombi is suggested by the frequency of thrombosis in patients who are immobilized in bed as a result of surgery, parturition, or trauma, in patients with congestive heart failure, and in persons with varicose veins. Associated with slowing of blood flow there may be settling of its suspended particles, or "sludging," a phenomenon that has been well demonstrated experimentally by Knisely and his associates.[7] However, the exact role of "sludging" as a mechanism of thrombosis remains conjectural.

Hypercoagulable Blood

Numerous studies of the coagulation mechanism lend support to the concept of hypercoagulable states. Decreased responsiveness to heparin[8] and changes in standard tests of coagulation[9-11] have been reported in various thrombotic states, but most of the established clotting tests (coagulation time, prothrombin time, and prothrombin consumption) are not suited, by design, for the detection of hypercoagulability.

Expansion of knowledge of blood coagulation in recent years has been concerned principally with the nature of plasma thromboplastin and its formation. The suggestion of a relationship between increased coagulability and increased thromboplastic activity by several investigators[12,13] seems logical, since, in vitro at least, the formation of thromboplastin is the longest phase of clotting, requiring more time than all the subsequent steps of coagulation combined (Table). By means of the thromboplastin generation test (TGT), as designed by Biggs and Douglas,[14] it is possible to study the earlier phases of coagulation. With the thromboplastin generation test or a modification of it,[15] evidence for hypercoagulability has been found in both idiopathic[16] and secondary thrombophlebitis,[17] in acute ar-

TABLE I
Scheme of Blood Coagulation

Step 1.	Generation of thromboplastin	Hageman Factor (XII) Plasma thromboplastin antecedent (XI) Plasma thromboplastin component (IX) Antihemophilic globulin (VIII) $\Big\}$ + platelets $\xrightarrow{\text{Calcium}}$ Plasma thromboplastin
Step 2.	Activation of thromboplastin	Plasma thromboplastin $\xrightarrow[\text{Stable factor (VII)} \\ \text{Stuart factor (X)}]{\text{Calcium} \\ \text{Labile factor (V)}}$ Activated thromboplastin
Step 3.	Conversion of prothrombin	Prothrombin $\xrightarrow[\text{thromboplastin}]{\text{Activated}}$ Thrombin
Step 4.	Conversion of fibrinogen	Fibrinogen $\xrightarrow{\text{Thrombin}}$ Fibrin

terial thrombosis,[18] and in coronary artery disease.[19]

Studies of known coagulation factors have shown increases in the quantities of these factors in clinical conditions that predispose to thrombosis, but as yet there is no more than circumstantial evidence that increased amounts of a clotting factor can cause intravascular thrombosis. Following trauma or surgery the concentration of fibrinogen increases.[20] During pregnancy there is an increase in levels of stable factor (VII) or of Stuart factor[21] (X) or of both. Antihemophilic globulin (VIII) has been found to be increased in the postoperative state[17] and in patients with large or metastatic cancer,[17] chronic ulcerative colitis,[22] and coronary artery disease.[23] Excessive amounts of a previously unrecognized clotting activity, tentatively named thromboplastin generation accelerator (TGA), has been reported in some cases of idiopathic recurrent thrombophlebitis and in patients with acute arterial occlusion complicating arteriosclerosis obliterans.[24]

Finally, there is experimental evidence supporting the concept of hypercoagulability. It has been shown that serum contains an activity which, when the serum is infused systemically, will consistently produce thrombosis in isolated venous segments of animals.[25] Furthermore, this activity of serum has been shown to be related in some way to specific coagulation factors [Christmas factor (IX) and Hageman factor (XII)].

Although there is increasing evidence that hypercoagulable states may exist, due perhaps to multiple mechanisms, all authorities do not agree on this. Perhaps the best evidence for hypercoagulability is the efficacy of anticoagulant drugs in the prevention of thrombosis as well as in its treatment.

Management of Thrombosis

The principles of the management of intravascular thrombosis are probably best reviewed by a consideration of deep venous thrombosis. Before the definitive treatment of venous thromboembolism is discussed, it is important to stress the need for preventive measures. Clinical experience indicates that during the postoperative period after pelvic surgery, splenectomy, or abdominal operations for malignant disease, the incidence of venous thromboembolism is increased. Furthermore, patients with a history of venous thrombosis, or those with leg trauma, cardiac disease, malignant lesions, or obesity are more prone than other patients to experience venous thrombosis when immobilized in bed. In the aforementioned situations, in which an increased risk of venous thrombosis is present, measures to minimize venous stasis and prophylactic anticoagulant therapy are indicated (provided no contraindications exist).[26]

General Measures

The therapeutic program for deep venous thrombosis should include measures to relieve venous congestion and restore venous flow as well as measures to prevent further thrombosis and pulmonary embolism. There is agreement concerning such general measures as rest in bed, elevation of the involved extremity, and relief of pain; but there is no unanimity about definitive therapy, some advocating anticoagulant therapy, others thrombolytic therapy, and still others vein ligation.

Vein ligation, while appealing from the standpoint of preventing pulmonary embolism, offers no protection against further thrombosis in other sites. The dissolution of thrombi by lytic enzymes is a promising therapeutic approach to venous thrombosis; but at present, problems of laboratory control, dosage, and methods of inducing lysis are not sufficiently standardized to justify its routine use.[27]

Thrombectomy without Ligation

Thrombectomy without venous ligation followed by anticoagulant therapy has been advocated by several investigators for the treatment of acute iliofemoral thrombophlebitis.[28-30] After removal of the thrombus, relief of venous congestion has been observed. Postoperative anticoagulant therapy is administered to prevent re-thrombosis. Advocates of this procedure feel that the incidence of chronic venous insufficiency will be re-

Continued

duced, but whether results are superior to those obtained with conservative treatment with anticoagulants will require additional study.

Anticoagulant Therapy

Assuming the probable role of hypercoagulability in the pathogenesis of thrombosis, anticoagulant therapy has, in our opinion, distinct advantages over the other methods of treatment. Not only should an adequate anticoagulant effect prevent further thrombosis, but there is evidence that anticoagulant therapy also hastens the recanalization of the thrombus. The use of anticoagulant drugs carries the hazard of bleeding; but sufficient experience with these drugs has been accumulated to minimize this complication, provided dosage is regulated by adequate laboratory tests.

Heparin is a mucopolysaccharide that exerts its anticoagulant effect immediately on contact with blood. The anticoagulant effect of heparin results mainly from its antithrombin action (Table) ; in addition, heparin appears to inhibit the earlier stages of clotting and to reduce platelet adhesiveness; and, since it carries a strong negative charge, heparin may impede thrombosis by altering the electrical potential of blood. Since heparin must be administered parenterally, and since its effect is dissipated relatively rapidly, it is best suited to short-term use when an immediate anticoagulant effect is desired.

The other group of anticoagulant drugs, the coumarin and indandione derivatives, are usually administered orally, and they differ from heparin in several other ways. These drugs exert their anticoagulant effect by depressing the levels of stable factor (VII), Stuart factor (X), Christmas factor (IX), and prothrombin (II) (Table). Following the administration of an adequate dose of one of the orally administered anticoagulant drugs, there is a period of 24 to 48 hours before the full effect is manifest; a similar lag occurs when administration of these drugs is discontinued. Of paramount importance in the use of the oral anticoagulant drugs is the availability of adequate laboratory facilities for performance of the prothrombin time, the test most widely used to control the dosage of these drugs.

Not uncommonly in the treatment of acute venous thrombosis we employ both heparin (for its immediate effect) and an orally administered anticoagulant at the onset. When adequate anticoagulant effect from the oral anticoagulant has been established, use of the heparin is discontinued and anticoagulation is maintained with the oral agent. The various orally administered anticoagulant drugs, their dosage, and the contraindications to their use have been discussed elsewhere in detail.[31,32,33]

Short-term anticoagulant therapy has been effective not only in the treatment of venous thromboembolism but also in the prevention of subsequent thromboembolic episodes in patients who have had previous venous thrombosis. Anticoagulant therapy is basic in the management of thrombotic disease, and its efficacy lends support to the concept that hypercoagulability of the blood is an important factor in the occurrence of intravascular thrombosis.

Summary

A rational approach to the management of intravascular thrombosis should be developed on the basis of its etiology. Unfortunately, the mechanism of thrombosis is not completely understood; however, changes in the blood vessel, flow, and coagulability all appear to have some role. In recent years, there has been increasing evidence for the probable importance of increased blood coagulability in thrombotic disease. For this reason, the anticoagulant drugs seem basic in both definitive and prophylactic therapy of thrombosis.

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Abstracts, Briefs and Commentaries

PATHOGENIC MICRO-ORGANISMS

Although everyone is exposed to pathogenic micro-organisms many times every day, the incidence of infectious diseases is relatively low. It is accepted that the host-parasite relationship determines the eventual occurrence and course of most infectious illnesses and that many environmental and genetic factors are implicated in their epidemiology. Psychological factors have also been suggested as etiologic determinants, but, because it is difficult to control or measure such factors, human data are relatively sparse. In this investigation, the authors demonstrated that mice under psychological stress (periodic paired light and shock) had an increased susceptibility to Coxsackie B virus, as measured by variations in body weight. This particular series of experiments exquisitely illustrates the principle of multifactorial etiology even in such seemingly straightforward problems as infectious diseases. The concept of multifactorial etiology is probably important in many areas of medicine, and psychological factors probably participate in many illnesses that have an ostensibly organic etiology.

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Friedman, S. B., Aden, R., and Glasbow, L. A.: Effects of Psychological Stress in Adult Mice Inoculated with Coxsackie B Viruses. Psychosom Med 27:361, 1965.

GASTRIC FREEZING FOR DUODENAL ULCER

Since 1962 there have been conflicting opinions in regard to the benefit of gastric freezing for duodenal ulcer. For a time it was thought that the extent of the freezing might be a factor in providing beneficial results. Scott and co-workers in Nashville, Tennessee, studied a series of 60 patients and classified their results into three groups, depending on the extent of the temperature of the returning coolant.

In most instances all patients obtained initial symptomatic relief despite the fact that there was no significant suppression of the gastric acidity.

Continued

Approximately one third of the patients required subsequent operation for recurrent or persistent symptoms. It was considered that gastric freezing in its present form would never replace definitive surgical intervention in the treatment of chronic duodenal ulcer.

It would seem that gastric freezing for duodenal ulcer should be carried out only in institutions where clinical research can be fully evaluated. It has no place in the armamentarium of the physician who is in private practice.

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Scott, William H., O'Neill, James A., Snyder, Harold E., and Shull, Harrison J.: An Evaluation of the Long Term Results of Gastric Freezing for Duodenal Ulcer. Surg Gynec Obstet 121:723, 1965.

GASTRECTOMY IN INFANCY AND CHILDHOOD

This paper was prompted by the little known hazards and indications for gastrectomy in infancy and childhood. Most of the apprehension concerning gastrectomy in childhood is based on gastrectomy in adults. The only experimental study of the problem was done by Thompson, Bonta, and Chatworthy in 1956, who found that healthy puppies subjected to 50% gastrectomy, vagotomy, and gastroduodenostomy at three weeks of age gained weight the same as control litter mates.

Data were furnished by a questionnaire sent to the American Academy of Pediatrics and the British Association of Pediatric Surgeons, an international group. Information concerning 113 gastric resections during the first 12 years of life was collected. There were 98 resections with ten per cent operative deaths. There were three late deaths due to cancer. Ninety-eight resections were done in the first two years of life. All ten deaths were in patients six years of age or younger, five of whom were four months of age or younger. Ninety-eight resections were subtotal distal or total and fifteen were esophagogastric.

Indications for resection were peptic ulcer (42 cases), gastric scarring or perforation resulting from ingestion of toxic material, lye or caustics (13 cases), duplication of the stomach (11 cases), and benign and malignant neoplasms (7 cases each). All but one of 15 esophagogastric resections were carried out for esophageal varices or esophagitis complicating hiatal hernia. There were two operative deaths. The lesions leading to operation in all fatal cases were bleeding, perforation, or both. The most significant finding of this study was the consistently normal growth and development following distal subtotal gastric resection or even total gastrectomy. Resection involving the cardioesophageal junction on the other hand was associated with a high degree of retardation of growth and development.

The Billroth type of reconstruction was most often used and comprised 83% of operations performed for peptic ulcer. Peptic esophagitis and "tampering" with the cardioesophageal junction were poorly tolerated by the growing child.

There was insufficient experience in this survey to assess the role of added vagotomy. The known high incidence of marginal ulceration in infants with peptic ulcer managed by gastroenterostomy alone suggests that vagotomy and antrectomy may be indicated.

Discussion

This international survey may be the first one of its kind. It is interesting to note that gastric surgery can be tolerated in infancy and childhood.

There are several pages of charts and tables giving minute details of age, operation, etc. I am much impressed by this excellent review.

Stanley R. Maxeiner, Sr., M.D.
Minneapolis, Minnesota

Moore, Thomas C.: Results of International Survey. From the Department of Surgery, University of Kentucky Medical Center, Lexington, Kentucky. Ann Surg 162, 1965.

BLEPHARITIS

The great variety of medication suggested for blepharitis reflects our essential ignorance of specific etiology. While the authors declare that they do not wish to discourage the search for specific agents, they feel that their own experience as well as that of others indicates that such specificity seldom will be found. Two general types encompass the vast majority of lid inflammation seen in general practice: seborrheic and ulcerative. In the seborrheic type the lid is reddened, with dry or greasy scales at the base of the lashes; in the ulcerative, the lid border is reddened, more in some spots than others, often with small pustules and loss of lashes. Because specificity has not been established, the authors feel that management should stress adequate lid hygiene, and they report a study of a series of 30 cases treated solely with a preparation combining antiseptic and keratolytic agents with sodium versenate (Blef-Dome, Dome Chemical Co.) The rationale on which its use is based is the penetration of cells by the chelating agent to permit lower concentrations of the antiseptic and keratolytic agents. Results showed that the majority of patients with uncomplicated blepharitis of the seborrheic type were sufficiently improved so that the frequency of medication could be reduced from twice daily to once every week or two, provided hygienic care was maintained. The ulcerative type responded more slowly; nevertheless, signs and symptoms diminished progressively with diligent care and therapy. In patients with blepharitis of the ulcerative type, treatment must be virtually unremitting, with daily attention to the eyelids.

The patients came from private practice and the general ophthalmology clinic of a medical center. The authors tabulate the cultures of organisms occurring singly and in combination taken from scrapings of the lids of these patients before and after therapy. After the bacterial studies were completed the patients were told to place the ointment on a cotton-wound toothpick with which they were to massage the lid margins and the roots of the eyelashes morning and evening. The treatment was to continue until all the scales were removed. Therapy was carried out twice daily until the lid margins were clean. After that, the massage was carried out once a day; then once every other day; then as required. No antibiotics, steroids, or other medications were used in any patient.

After therapy the number of patients with normal lid flora increased from 8 to 24. The authors tabulate the complete list of before-and-after cultures from eyelid scrapings, not repeated here. Tolerance to medication was excellent. Over a two-and-a-half year period only 2 cases of lid sensitivity have been seen out of a total of over 250 patients treated. The sensitivities disappeared when the drug was stopped.

Courtesy of Medical Abstract Service
Berwyn, Illinois

Galin, Miles, Berger, Robert: New York J Med 62:2965, 1962.

CONTROL OF INFECTIONS IN HOSPITALS*

The occurrence of infections in hospitals is of deep concern to patient, physician and hospital administrator. The sporadic occurrences of infections in nurseries and nursing mothers and the fairly frequent occurrence of infections in supposedly clean surgical cases confirm the fact that the problem of hospital infections is still with us and requires constant vigilance for their limitation and control. Therefore, the Joint Commission on Accreditation of Hospitals in August, 1958, recommended that every hospital have an "Infection Committee" charged with the responsibility of investigation, control, and prevention of infections within hospitals. An attempt to evaluate the degree of compliance and success of such "set-ups" in Minnesota hospitals has been made through the distribution of a questionnaire to 45 hospitals in Minnesota — each containing 100 or more beds. The replies indicate that, in general, a serious attempt to comply with the recommendations made by the Commission on Accreditation of Hospitals has been made by the 36 hospitals answering such questionnaire. Several weaknesses and deficiencies in these "set-ups" and recommendations for their correction are made by the writer. Such recommendations include (1) the granting of regulatory powers to the "Infection Committee," (2) the elimination of added charges for isolation to those patients contracting infections in hospitals after their admission as a "clean case," and (3) setting up of larger "area" infection control committees made up of representatives of each individual hospital's infection committee, local and state health departments, and the medical society for the purpose of determining basic measures of detecting and reporting on infectibility and the control of infections in that area. Such measures, the writer feels, are in accord with the recommendations made by the "Accreditation of Hospitals" committee and could well be the added procedures needed to more completely minimize infections occurring in our hospitals.

Alex Berger, M.D.
Minneapolis, Minnesota

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*Submitted elsewhere for publication.

VENOM FATALITIES

There were 460 fatalities from venomous animals in the United States from 1950 through 1959, an average of 46 deaths per year and an average annual death rate 0.28 per 1,000,000 population. *Hymenoptera* insects (bees, wasps, hornets, yellow-jackets, ants) killed 229 (50%) persons, poisonous snakes killed 138 (30%), and poisonous spiders killed 65 (14%). Scorpions, *Coelenterata,* stingrays, and unidentified venomous animals also caused deaths. Two spider bite deaths were caused by brown spiders *(Loxosceles recusus);* whereas *Latrodectus* spiders caused the other spider bite deaths. Usually several hours elapsed before people died from bites by venomous snakes and spiders. Most deaths from *Hymenoptera* insect stings took place within one hour and resulted from insect allergy. Most fatalities from venomous animals happen from April through October.

Courtesy of References and Reviews
Journal of the American Medical Association

Parrish, H.: Amer J Med Sci 245:129, 1963.

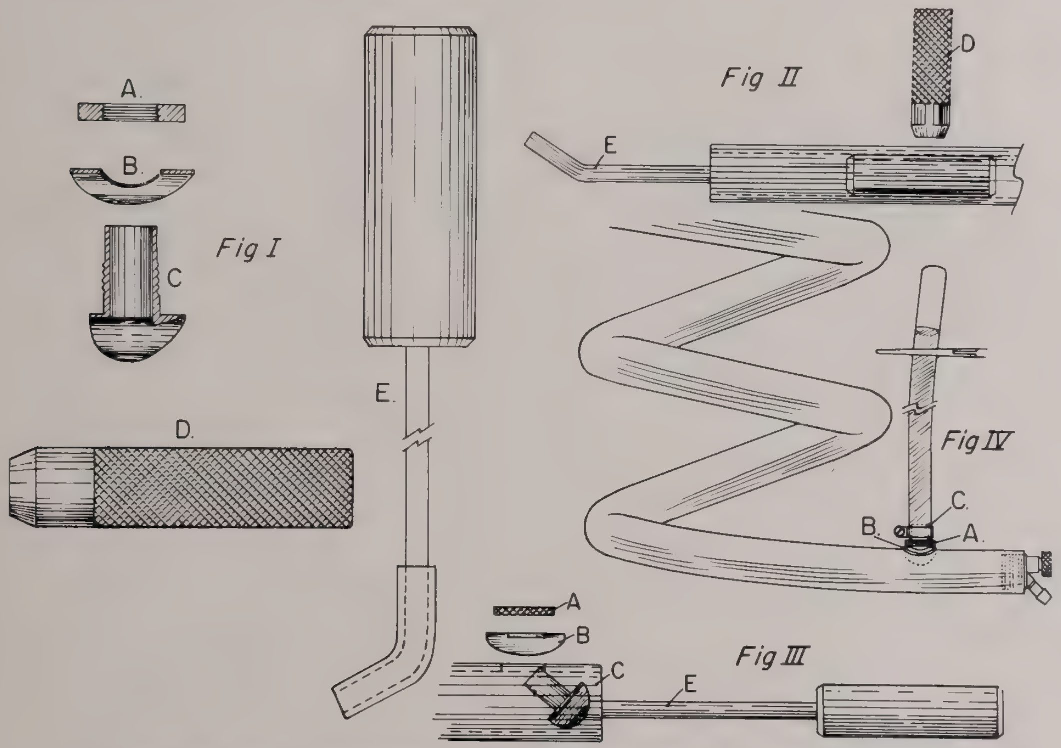
This Being of mine . . . consists of a little flesh, a little breath, and the ruling Reason. — Marcus Aurelius

The Physician's Workshop

*Bubble Trap for the Helix**

Arterial air embolism remains a definite hazard during extracorporeal circulation and open heart surgery.[1-4] One source of systemic air embolism is the extracorporeal unit. "High flows" increase the possibility that microair bubbles may form and not be effectively removed by the unit before the blood enters into the patient's vascular system. Extracorporeal units have been designed so as to minimize this possibility of air embolism.

We have utilized the DeWall-Zuhdi bubble oxygenator-helix reservoir system and arterial blood flows of 2.2-2.4 liters per square meter of body surface for open heart procedures. Our experience has been most satisfactory. Our confidence has been further heightened by a modification of the helix which effectively diminishes the possibility of air embolism from the apparatus per se. This modification can be termed a "bubble trap" (Figure).



The stainless steel components of the bubble trap are pictured in the upper left corner (Figure I). "C" is a ½" cylinder threaded in the middle ⅓ of its 1.9 cm. length. The cylinder is mounted on a 3.5 cm. diameter disk which is 3 mm. thick and curved to match the curvature of the helix tubing. This curved disk is tapered to its edges so as to fit flush when in place in the helix. The distal side of the ½" cylinder is 3 mm. lower than the proximal side. Direction of flow — left to right.

"B" is a washer with a hole to admit the ½" cylinder of C and curved to match the curvature of C. "A" is a lock nut to hold the tubing of the helix securely between C and B. "D" and "E" of Figure 2 are tools used in the preparation and placement of the bubble trap in the helix. After threading the helix tubing on the Zuhdi coil and marking the bubble trap location 18 cm. from the distal end, the tubing is backed off approxi-

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*Supported in part by the Mount Sinai Hospital Women's Auxiliary Fund.

Editor's Note: In this section of MINNESOTA MEDICINE we are introducing new ideas; new instruments or mechanical devices; procedures, diagnostic techniques, etc. Share your medical secrets with your colleagues.

Continued

mately 40 cm. The plastic handle of E (Figure II) is adjusted to the bubble trap mark. A ½" hole is bored with the cork borer D. The tip of the 20 cm. shaft of E is curved and covered with ¼" O.D. x 3/16" wall geon tubing. Component C of the bubble trap is placed on this curved end of E and pushed through the hole in the helix tubing (Figure III). B is now positioned and secured in place with lock nut A. The helix tubing is threaded back on the Zuhdi coil. A 75 cm. length of ½" tubing is fitted on C and secured with a small hose clamp. After priming the helix, the 75 cm. length of ½" tubing is clamped just below the fluid level. The assembled bubble trap is shown in Figure IV.

It is the common experience of those who utilize the DeWall-Zuhdi unit that small, stable bubble patches collect on the blood in the helix. The rate of bubble formation is related to the blood flow and the amount of blood returned to the system via the cardiotomy suction wells. As one to five-millimeter patches, the bubbles migrate slowly toward the lower opening of the helix. The bubble patches rarely migrate to the outflow opening of the helix. If they do, it is unlikely they would be carried out in the arterialized blood, since they float. It is, however, not unreasonable to assume that due to small eddy currents, micro bubbles could be stripped from the main patch and be forced into the outflow stream. The bubble trap stops the bubble patches at a level where it is virtually impossible for this to occur.

The bubble trap, a 75-cm. vertical length of 0.5-inch-diameter tubing, is placed 18 cm. from the outflow end of the helix. The trap is designed to cause a minimum of turbulence in this area of relatively low flow. This low flow results because the cross sectional area of the helix is greater than the arterial line and has considerably less peripheral flow than the flow at the core of the helix.

We have never observed a bubble patch bypassing the bubble trap. On several occasions, as bubble patches have approached the trap, we have observed not only these bubbles but also bubbles not apparently associated with the main patch floating to the surface of the 75-cm. length of 0.5-inch-diameter tubing. We have trapped up to 3 ml. of bubbles in this manner and, therefore, feel the added safety is more than adequate compensation for its use.

Summary

Attached to the DeWall-Zuhdi helix, a single vertical 0.5-inch-diameter tubing has served as an effective bubble trap.

T. Gunther, B.S.*
G. Hughs**
J. T. Grismer, M.D.†
Minneapolis, Minnesota

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*Supervisor, Cardiopulmonary Laboratory; Member, American Society of Extracorporeal Technicians.

**Chief, Technician, Phalen Manufacturing Company.

†Director, Cardiopulmonary Department, Mount Sinai Hospital and Thoracic Surgeon, St. Louis Park Medical Center.

We wish to acknowledge the invaluable assistance of Mr. Earl Levens and Mr. John Deprez, Extracorporeal Technicians.

References

1. Goldfarb, D., and Bahnson, H. T.: Early and Late Effects on the Heart of Small Amounts of Air in the Coronary Circulation. J Thor Cardiov Surg 46:368, 1963.

2-4 May be secured from the author or the reprints.

Don't ask for what you'll wish you hadn't got. — Seneca

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512214

1. Torosdag, S., Schvartz, N., Fletcher, L., Fertig, H., Schwartz, M. S., Quan, R. F. B., and Bryant, J. M., Pargyline Hydrochloride as an Antihypertensive Agent With and Without A Thiazide, Am. J. Cardiol., 12:822, Dec., 1963.

2. Pollack, P. J., Pargyline Hydrochloride and Methyclothiazide Combined In The Treatment of Hypertension, Cur. Thera. Res., 7:10, Jan., 1965.

3. Bryant, J. M. et al., Antihypertensive Properties of Pargyline Hydrochloride, New Non-Hydrazine Monoamine Oxidase Inhibitor Compared with Sulphonamide Diuretics, J.A.M.A., 178; 406, Oct., 1961.

BP reductions in the recumbent and sitting positions often are nearly as great as in the standing. In clinical trials, the average *recumbent* BP reduction was 36/18 mm. Hg.

The average *standing* reduction in clinical trials was 45/22 mm. Hg. Thus the difference between the standing and recumbent readings was only 9/4 mm. Hg.

Significantly lowers blood pressure in all body positions; less likelihood of orthostatic hypotension

In clinical trials, the average reduction in standing blood pressure was 45/22 mm. Hg.; in the sitting position it was 48/20 mm. Hg.; and in the recumbent position, 36/18 mm. Hg.

Because Eutron effectively reduces blood pressure in all body positions, there is reduced likelihood of orthostatic symptoms or hypotension.

This was reflected in the relatively mild character of side effects seen in clinical trials (see below).

Smooth and gradual onset

Onset of antihypertensive action is usually quite smooth. Initial reduction of systolic and diastolic readings is usually seen within a week – maximum reduction in seven to ten days.

Less troublesome side effects may be seen; frequent improvement in "sense of well-being"

Fewer than 1% of patients studied discontinued Eutron therapy because of side effects. This is due in part to the relatively low dosage needed with the combination. Usual recommended dose is one tablet daily—that is, 25 mg. Eutonyl with 5 mg. Enduron. *This is about half the usual therapeutic dose of Eutonyl given alone.* As a consequence side effects may be milder. And, as with Eutonyl given alone, the patient may well note an increased sense of well being. This is in distinct contrast to most other antihypertensive therapy.

ABBOTT

Prescribing information for
EUTRON

INDICATIONS: Eutron (pargyline hydrochloride and methyclothiazide) is indicated in the treatment of patients with moderate to severe hypertension, especially those with severe diastolic hypertension. It is not recommended for use in patients with mild or labile hypertension amenable to therapy with sedatives and/or thiazide diuretics alone.

CONTRAINDICATIONS: Eutron is contraindicated in patients with pheochromocytoma, advanced renal disease, paranoid schizophrenia and hyperthyroidism. Until further experience is gained it cannot be recommended for use in patients with malignant hypertension, children (under 12 years of age), or pregnant patients.

The concomitant use of the following is contraindicated: other monoamine oxidase inhibitors; parenteral forms of reserpine or guanethidine; sympathomimetic drugs; foods high in tyramine such as cheese; imipramine and amitriptyline, or similar antidepressants; methyldopa. A drug-free interval of two weeks should separate therapy and use of these agents.

WARNINGS: Pargyline hydrochloride is a monoamine oxidase inhibitor. Patients should be warned against eating cheese, and using alcohol, proprietary drugs or other medication without the knowledge of the physician. When it is necessary to administer alcohol, narcotics (notably meperidine), antihistamines, anesthetics, barbiturates and other hypnotics, sedatives, tranquilizers, or caffeine, these agents can be used cautiously at a dosage of ¼ to ⅕ the usual amount. Avoid parenteral administration where possible. Withdraw pargyline two weeks before elective surgery.

Patients should be warned about the possibility of postural orthostatic hypotension. Those with angina or other evidence of coronary disease should not increase physical activity. Pargyline may lower blood sugar. Potassium depletion is unlikely at the recommended dosage, but if it occurs, adjust dosage or withdraw or provide added natural food sources of potassium; potassium tablets should be avoided wherever possible, as bleeding or obstructive ulceration of the small bowel has been associated with their use; potassium levels should be especially watched if the patient is on digitalis or steroids, or if hepatic coma is impending.

PRECAUTIONS: When determining the antihypertensive effect of Eutron, blood pressure should be measured while the patient is *standing*. Use with caution in hyperactive or hyperexcitable persons. Such persons may show increased restlessness and agitation. Withdraw drug during acute febrile illness. Watch patients with impaired renal function for increasing drug effects or elevation of BUN and other evidence of progressive renal failure; withdraw drug if such alterations persist and progress. Pargyline has not been shown to cause damage to body organs or systems. As with all new drugs, complete blood counts, urinalyses, and liver function tests should be performed periodically. The drug should be used with caution in patients with liver dysfunction. With prolonged therapy, examine patients for change in color perception, visual fields, and fundi.

Elevated blood urea nitrogen, serum uric acid or blood sugar are possibilities attributable to the methyclothiazide in Eutron. Methyclothiazide may also reduce arterial response to pressor amines. Blood dyscrasias, including thrombocytopemia with purpura, agranulocytosis and aplastic anemia, have been seen with thiazide drugs.

SIDE EFFECTS: The use of pargyline may be associated with orthostatic hypotension. Mild constipation, slight edema, dry mouth, sweating, increased appetite, arthralgia, nausea and vomiting, headache, insomnia, difficulty in micturition, nightmares, impotence, delayed ejaculation, rash, and purpura have been encountered with pargyline. Hyperexcitability, increased neuromuscular activity (muscle twitching) and other extra-pyramidal symptoms have been reported. Drug fever is extremely rare. Congestive heart failure has been reported in a few patients with reduced cardiac reserve. Nocturia has been observed with the combination. If side effects persist, despite symptomatic therapy or reduction of the dose, discontinue the drug.

ABBOTT

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Book Reviews

Some books are to be tasted, others to be swallowed, and some few to be chewed and digested. — Bacon

MODERN TREATMENT — **Vol. 2, No. 4, July 1965, Harper and Row.**

This issue concerns the treatment of Diabetes Mellitus and the Emergency Treatment of Trauma. Both sections are well written. The section on diabetes is detailed enough so that it is valuable as a reference, whereas the section on trauma, covering such a large subject, is less detailed. A general discussion of fractures is not included.

The issue (a bimonthly publication) is paper bound and suitable for browsing and review.

Harrison H. Farley, M.D.
Minneapolis, Minnesota

A PRIMER OF WATER, ELECTROLYTE AND ACID BASE SYNDROMES, **3rd edition — Emanuel Goldberger, Lea and Febiger, 1965, 410 pages.**

This is a revised edition of a book which has been well received by clinicians. Diagnostic and therapeutic considerations in management of the disorders of water, electrolyte and acid base in patients are presented. Although the text does not go into great detail on the physiologic considerations in these disorders, enough is presented to make the clinical problems understandable, both as to manifestations and their management.

I found the book well written, clear in its presentation and extremely useful in its application to clinical problems. It is recommended as a very practical and quick reference text for the clinician.

Alvin L. Schultz, M.D.
Minneapolis, Minnesota

SYNOPSIS OF CARDIOLOGY — **W. I. Gefter, B. H. Pastor, R. M. Myerson, C. V. Mosby Co., St. Louis, Missouri, 1965. 839 pages; price $9.85.**

A simple classification of medical books is this trichotomy: big, thick texts for medical students; large thin monographs for specialists; and small, pocket-sized books for house staff. **Synopsis Of Cardiology** measures 5 by 8 inches, and its 800 odd pages will form a respectable bulge in the pocket of the interne on medicine, who, I suspect is the target at whom the author aimed in his preparation of this synopsis. There are six sections covering the cardiovascular examination, heart failure, arrhythmias, types of heart disease, diseases of the vascular system, and special problems. The section on cardiovascular examination includes an excellent resume of electrocardiography and cardiac roentgenology. It is surprising that chapters on cardiac catheterization and angiocardiography, so essential in present day cardiovascular studies, are omitted.

The discussion of types of cardiac disease and their treatment is uniformly good. Pastor, who contributes some excellent chapters, emphasizes the value of "bloodless" phlebotomy, rotating tourniquets in severe heart failure. He also mentions many helpful measures to be undertaken in intractable failure. As for venesection in heart failure, he would use it in congestive heart failure associated with polycythemia, that is, perhaps only once in a lifetime of cardiological practice. But this would shelve a useful tool in the treatment of acute heart failure, especially acute pulmonary edema, when venesection can be lifesaving (as is elsewhere stated in the book).

Reuben Berman, M.D.
Minneapolis, Minnesota

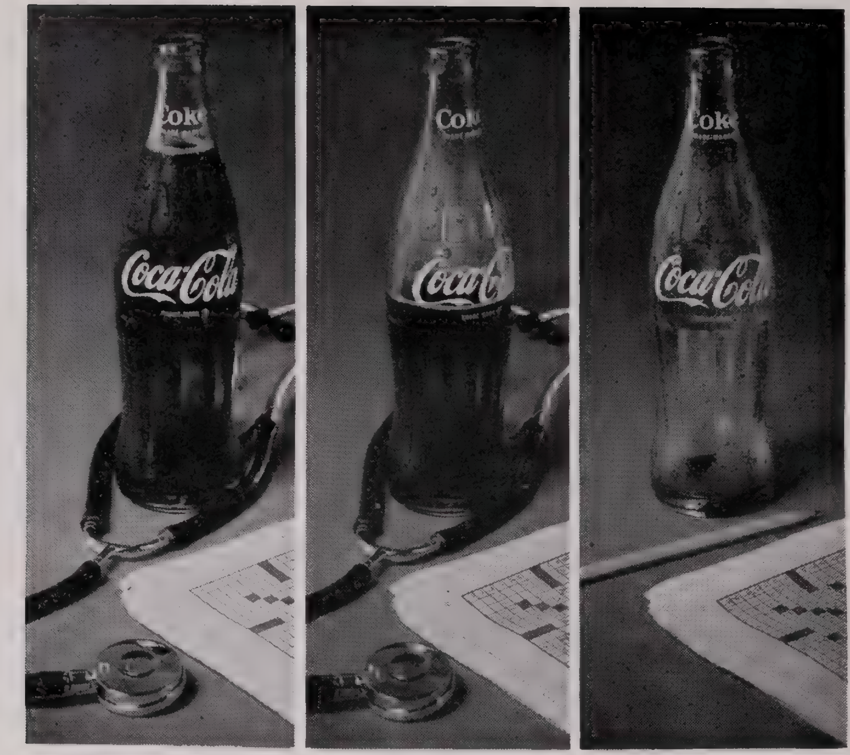
ANATOMY AND SURGICAL TECHNIQUE OF GROIN DISSECTION — **Shieber and Dillard, C. V. Mosby Company, St. Louis. Price $9.75, 97 pages, 36 illustrations.**

Groin dissection is indicated in malignancies of the vulva, anus, penis, and of the lower extremities. Almost the only exception would be extremely small lesions of the vulva, small epidermoid carcinomas arising from burn scars, osteomyelitis, or stasis ulcers, and small lesions of the anal canal. A clarification of these exceptions is detailed in the monograph.

The technique of the procedure is reasonably well illustrated with wash type drawings; and for the surgeon who would be attempting to view this procedure, the illustrations are sufficiently adequate.

This well bound monograph is worth possessing.

Carl O. Rice, M.D.
Minneapolis, Minnesota



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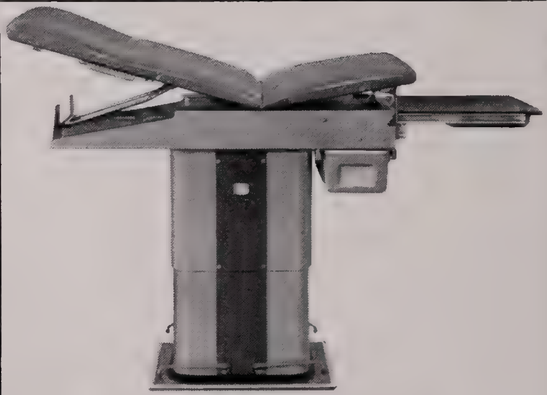

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Gleanings from the Meetings

Minnesota Surgical Society
November 5, 1965
Minneapolis, Minnesota

The Minnesota Surgical Society met for its semi-annual meeting on November 5, 1965. Dr. William ReMine, President, and Dr. Stuart W. Arhelger, Program Chairman, had arranged an excellent series of scientific papers.

Zollinger-Ellison Syndrome

The guest speaker, Dr. Stanley R. Friesen, Professor of Surgery at the University of Kansas Medical School, delivered the main address of the session on the subject "Evolution of Diagnosis and Management of the Zollinger-Ellison Syndrome,"* In addition to the usual hypersecretion and recurrent ulceration, several identifying features were noted as suggestive or diagnostic of the disorder. He found common occurrence of hyperrugation** in the stomach or in a residual pouch, gross nodularity of the duodenum, steatorrhea, and 12-hour gastric secretion of at least one liter containing more than 100 mEq/L of hydrochloric acid. Only occasionally was he unable to find the primary lesion in the pancreas despite the presence of metastatic lymph nodes and other areas of metastasis. Chemical analysis revealed a gastrin-like substance from the tumor of all but one of the cases.

He found that a total gastrectomy controlled the disease, and even in the presence of metastases the removal of the target organ effectively prolonged life for several years.

Portacaval Shunt

Dr. Martin A. Adson presented his experience with emergency portacaval shunt for bleeding esophageal varices. Very commendable mortality figures were presented, even though some patients with encephalopathy and some with intense jaundice were included in his series. Adson makes the point that jaundice in the alcoholic cirrhotic greatly increases surgical risk, whereas this is not necessarily true in the cholestatic jaundice of posthepatitic or biliary cirrhosis. A direct portacaval shunt is preferred in the emergency situation. However, splenorenal shunts, elected for technical reasons, also controlled hemorrhage from varices.

Aorta-jejunal Fistula

Dr. Richard E. Larson presented a rather astounding case of upper

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*See Minnesota Med 46:864, 1963.

**See Test Your Word Score Page 271.

Continued

gastrointestinal bleeding due to aorta-jejunal fistula. The fistula had developed at the upper end of a nylon prosthesis which had been implanted five years previously. This complication was technically controlled by inserting a new bifurcation prosthesis and oversewing the proximal end of the old graft just distal to the fistula. This was again followed in a few months with recurrences of gastrointestinal bleeding from reestablishment of a fistula originating from the distal end of the old graft which had not been removed. He makes the point from this recurrent episode that, in spite of the technical difficulties, further degeneration of the remaining old graft can lead again to such difficulties, and he therefore recommends removal and replacement rather than closure and bypass.

Operation for Hypercholesterolemia

Dr. Henry Buchwald, Department of Surgery, University of Minnesota Medical School Hospitals, won the first annual prize essay and presented his paper on the development of the ileal bypass operation as a potential therapeutic procedure in patients with hypercholesterolemia. The initial experimental studies were done in the rabbit and then in the pig, in order to test the thesis that cholesterol absorption occurs mainly in the ileum, and that if this area is bypassed, cholesterol absorption and secondary blood cholesterol could be reduced.

A blind loop of ileum about one third of the small intestine is produced and an end to side anastamosis of the proximal end of the ileum is made to the cecum. The first case was done two and a half years ago. Nineteen human cases have been done to the present time. These patients have some diarrhea initially but by three months have one to three stools per day, and have had no weight loss. They require Vitamin B_{12} parenterally every two months. Blood cholesterol levels have been reduced to normal or below (an average of 40%). Further studies are being conducted to ascertain clinical effectiveness and, in fact, the feasibility in the management of these patients.

Theoretical to Empirical

Until probably sometime during the thirteenth century, the anatomy that was taught to students of medicine was entirely of a theoretical nature, and what was worse, the theories themselves were often quite erroneous. It is believed that the practice of dissection of human bodies for classes in anatomy was started very likely sometime during the thirteenth century. However, it was not until several hundreds of years later that the student did any dissection himself. And even then there were often only two bodies to be dissected in a medical school during a school year. In the early days, the teacher lectured while sitting at his desk as a barber did the dissecting, and a demonstrator pointed out the various structures with a wand. It actually was a couple hundred years before the teacher had acquired enough energy to get off of his fanny and stand beside the cadaver to point out the structures himself.

— F. William Saul, M.D.: Pink Pills for Pale People

"This problem, when solved, will be simple."

— General Motors Research Department

Special Article

Forensic Psychiatry

M. ROBERT WILSON, JR., M.D.*
Rochester, Minnesota

SINCE MAN first formulated the principle of culpability — and its corollaries: punishment and deterrence — the concept of criminal responsibility has stimulated controversy, has provoked hostilities, schisms and revolutions, and has generated countless learned volumes. At present, psychiatry finds itself designated as the heir to the issue of this forced marriage of theology and jurisprudence. Before considering the duties, hazards, and consequences of such guardianship, it is useful to look at the evolution of this concept.

Evolution of Forensic Psychiatry

Those cradles of democracy, the Greek city states, were among the earliest civilizations to give legal recognition to the mitigating role man's passions and emotions should be accorded in the judicial process. Elaborate provisions to protect the emotionally disturbed from being punished for their misbehavior were incorporated into Plato's laws for a model society.

Doctrine of "Fatal Necessity"

Pesidonius the Stoic postulated a doctrine that closely parallels the contemporary concept of irresistible impulse; he designated it "fatal necessity" and frequently invoked it with success as a defense on behalf of his clients, further testimony to the cognizance of the importance ascribed to emotions in the delicate function of assessing responsibility in those early days.

The Elimination of Humanistic View

It is not surprising that, in the ensuing Dark Ages, one of the first virtues of that earlier democratic heritage to be eliminated was just this very humanistic view of responsibility, guilt, and punishment. In 429 A.D., a document titled the Codex Theodosinus proclaimed by fiat that magic was bad and criminal and that practice of it was illegal; the fatuous conclusion that insanity was both the cause and the consequence of sorcery was inevitable and forced the physician into abdicating his traditional role of healing men's minds as well as their bodies, leaving the former to the Church and the State. This persecution of the insane as willing agents for the legion of devils which invaded Christendom reached its height in the fifteenth century with the publication of *Malleus Maleficarum,* or *Witches Hammer,* by two friars, Henry Kramer and James Sprenger. In their monumental work these

Continued

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*From the Section of Psychiatry, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

zealous and scholarly ecclesiastics outlined the magnitude of the witchcraft problem, gave case reports of known instances of transvection and other equally deplorable manifestations of demonology, and prescribed the only satisfactory route to salvation: freeing the soul by destroying by fire its defamed tabernacle. The resistance to this radical text was widespread but was soon quieted when Pope Innocent VIII gave moral sanction and papal license to the friars' work in 1484.

Sick Minds the Bailiwick of Medicine

The effect of *Malleus Maleficarum* on the continuing exclusion of psychiatry from the forum of assessing human behavior was somewhat tangential to the main historic issues, but a survey of pertinent chronicles reveals that a few scientific voices were raised in an effort to return sick minds to the bailiwick of medicine. Johann Weyer, who lived from 1515 to 1588, was the most persistent and articulate of these, and he has been cited as the first truly humanistic medicolegal psychiatrist. Weyer wrote ardently and was intrepid in the exposition of his view that witches were sick people and should be turned over to physicians for care. He asserted that the confessions of accused witches and sorcerers were themselves a form of madness and that this behavior was hardly an expression of free will but, quite the contrary, was a form of illness. This was a view which no one would freely embrace. For his efforts he earned the distinction of having the titles of his books listed on the Catholic Index and escaped excommunication only through his otherwise exemplary adherence to church dogma. Among his lay antagonists the most vitriolic was Jean Bodin, an attorney, who issued an extensive rebuttal of Weyer's views. He claimed that a physician should not be allowed to trespass into the sanctuary of the courts, and he was widely supported by most of his colleagues. "If Weyer's sophisms . . . held good, the thieves and robbers might always appeal for mercy by blaming the devils for their deeds . . ."[1] reads one passage which characterizes much of Bodin's argument.

Faced thus with certain censure and calumny, few of Weyer's colleagues dared support him, and some indeed even denounced him; the views that Weyer espoused died with him and remained dormant for nearly a century. The succeeding chapters in the chronicle of the role insanity should play in tempering the assigning of responsibility were written in Great Britain, where a judiciary unfettered by the influences of Kramer and Sprenger was slowly deliberating the question of a humanistic application of the law. In the early part of the seventeenth century the English jurist, Lord Hale, ruled that the existence of insanity was a valid defense in considerations of responsibility for criminal acts, but he devoted his attention to the concept of partial insanity, it being his allegation that the latter is not an adequate defense. For Lord Hale, the accused must have been stark raving mad at the time of the crime to be exculpated; anything short of this was insufficient. Few persons were acquitted. Lord Hale's views served as precedent throughout England for nearly 200 years.

Hadfield Decision: The Beginning of Forensic Psychiatry

In 1800, the trial of a man named Hadfield, charged with shooting at King George III in London's Drury Lane Theatre, marked a significant milestone for forensic psychiatry. The defense counsel, Mr. Erskine, defined for the jury, for the first time in an English court of law, the concept of delusional thinking; he argued that his client had fired on the sovereign as a consequence of such a delusion, and he won for him an acquittal. This was, however, not the dawn of enlightenment that it should have been. In 1812, another man, Bellingham, was found guilty of murder (of the Hon. Spencer Perceval) even though his counsel clearly showed that he was delusional. In his charge to the jury, the Lord Chief Justice ignored the Hadfield decision and emphasized the issue of cognition as a test for insanity — that is, did the defendant know right from wrong. These knowledge tests, based on the Bellingham decision, won widespread acceptance and constituted the prevailing English view on the matter of insanity for several decades.

What Is Insanity

In the nineteenth century a chorus of voices was heard tardily promoting the views of Johann Weyer. In France, Pinel endeavored to show that intellect was not the sole decisive factor governing man's behavior, and Esquirol wrote a treatise establishing that insanity can exist without concurrent delirium. Tuke proposed the concept of inhibitory insanity, which asserted that all madness was a consequence of decreased inhibition in one sphere or another of the mind. Prichard described "moral insanity," and other physicians in England, in Europe, and in the United States attempted to point out that the prevailing concept of cognitive tests was not adequate to establish or refute the existence of insanity. The furor surrounding the whole issue of insanity finally compelled the English House of Lords, in 1843, to examine the situation and, hopefully, clarify it.

The McNaughton Rule

In that year there occurred the celebrated trial of a Scotchman, David McNaughton, who was charged with murder (of a man named Drummond, private secretary to Sir Robert Peel, the Prime Minister). McNaughton harbored delusional beliefs that he was being persecuted by the Prime Minister and killed Drummond by mistake. The trial judge, in his charge to the jury, acceded to defense counsel's claims and supported the view that McNaughton was insane, outlining a test for insanity which has since been referred to as the McNaughton rule. The accused was acquitted of the charge, which generated heated controversy. One view was most acridly stated by the queen, Victoria, who allegedly remarked that anyone who wanted to kill Sir Robert could hardly be judged insane. In their investigation, the Lords approved the test in McNaughton's case and recommended that it become established precedent for future cases. In its approved version, the McNaughton rule states the following:[2] "To establish a defense on the ground of insanity, it must be clearly proved that, at the time of committing the act, the party accused was labouring under such a defect of reason, from disease of the mind, as not to know the nature and quality of the act he was doing, or, if he did know it . . . he did not know he was doing what was wrong." The Lords added that the question of right and wrong should be put in reference to the particular act with which the accused is charged.

The McNaughton rule thus incorporated both the cognition test and a principle which went beyond mere knowledge of right and wrong. This too represented an unsatisfactory ultimate solution to the problem of criminal responsibility, but it did effectively bring some consistency to the common law on the subject. Dr. Isaac Ray, prominent American psychiatrist, was among the many critics of the McNaughton rule; in his book *Medical Jurisprudence of Insanity* (1871),[3] he lamented the efforts by jurists to identify the *sine qua non* of mental illness and urged them to accept the concept of insanity as a disease which, in consort with other distempers, requires the application of many tests by specialists to effect an accurate diagnosis. Rather than heeding this advice, the jurists continued their search for a pathognomonic test to ascertain the presence or absence of insanity.

Irresistible Impulse

Shortly after the publication of Ray's second edition, Shaw (Chief Justice of Massachusetts) and Gibson (Chief Justice of Pennsylvania) dusted off Pesidonius' long-dormant doctrine of fatal necessity, christened it "irresistible impulse," and sought for general endorsement of it as that *sine qua non* whose very existence Ray had labeled chimeric. "Irresistible impulse" did win a limited acceptance, and in some jurisdictions it was added to the McNaughton rule as a footnote; at the present time it is incorporated into the legal codes of 17 states and has been accepted by the United States Supreme Court.

Shortcomings of McNaughton Rule

The McNaughton rule clearly limits testi-

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mony to certain specific features of mental illness, and, since consideration of other features which we all recognize as pertinent in the assay of insanity is in violation of the rule, the psychiatrist testifying in such a jurisdiction will be hampered in his attempt to describe for the jury the mental status of the accused. The inevitable consequence of this is that certain mentally ill persons will be found culpable and sentenced or even executed for acts which were a product of their illness and for which they should not be held responsible.

An instance of the use and abuse of psychiatry in a murder case was reported by Wiseman.[4] The defendant, who was accused of murdering his fiancée, was clearly psychotic, but defense testimony to the pertinent psychologic issues was precluded because of the McNaughton rule, while the use of psychiatric expertise by the prosecution within the scope of the rule left no choice for the jury but to find the defendant guilty. Even the prosecutor supported the family's appeal for gubernatorial clemency, recognizing in fact the accused's derangement; however, the defendant committed suicide in jail, affording graphic but tragic evidence for the validity of his defense, but obviating action on the plea.

The Durham Decision

Not all jurists ignored Ray's supplications; in New Hampshire in 1871, Judge Charles Doe presaged a broader and more sophisticated concept of insanity than had heretofore ever been espoused in a court of law when he charged a jury (in the case of State of New Hampshire vs. Jones) with the simple admonition that the defendant could not be found guilty of the murder of his wife if his act was the product of mental disease. Judge Doe incisively avoided prescribing tests based on one, two, or three mental functions and paid homage to the mosaic of man's mind, the loss of any piece of which can spoil the whole and of which no piece is endowed with superior status over another. But few jurisdictions accepted Judge Doe's farsighted philosophy.

In 1954, however, a far-reaching doctrine was postulated by Judge Bazelon of the United States Court of Appeals for Washington, D.C. In the trial of a man named Durham (for breaking and entering) because of a history of frequent past offenses which had led to acquittals based on insanity with subsequent commitments to a mental hospital, testimony to his chronic recidivism was allowed by the trial judge and accepted as good and adequate reason that insanity could not be permitted again as a defense. Durham was then found guilty. His appeal was heard by Judge Bazelon who ruled that an accused is not criminally responsible if his unlawful act was the product of mental illness or defect. This ruling has been called the Durham decision and has, in the past decade, along with the McNaughton rule and "irresistible impulse," composed American jurisprudence concerning insanity as a defense.

Allowing Discussion of Mental Illness

The spate of arguments concerning the Durham decision bespeaks the controversy that it has generated, and, in subsequent rulings, numerous efforts have been made to temper its implications. Certainly, this decision removed the fetters from psychiatric testimony by allowing discussion of mental illness without reference to any particular facet.

Prosecution Must Prove Sanity If It Is In Doubt

In fact, carried to its ultimate evolution, it switches the burden of proof from defense to prosecution, making it incumbent on the latter to establish the presence of sanity when this question is raised by the defense. Such a doubt can be introduced into almost any case with a minimum of effort. As meritorious as this decision is, praise must be tempered with a consideration of the total implication inherent in this precedent. Did Bazelon, as many of his detractors allege, throw out the baby with the bath water; does the Durham decision exculpate, by definition, our entire criminal population? Glueck,[2] in the Isaac Ray Lectures at Tulane University in 1961, presented an assessment of some of the more salient criticisms of the Durham decision.

Shortcomings of Durham Decision

The Durham decision has been attacked as being too vague in not providing the jury with explicit guides to the determination of insanity, whereas the McNaughton rule and the "irresistible impulse" concept furnish rigid formulae. In this sense the Durham decision clearly respects the complexity of mental illness and, while taxing the capacity of the juror to comprehend this, it does service to the cause of justice.

It has been attacked as a menace to law enforcement; its critics claim that it will permit the acquittal of any accused lawbreaker. However, the facts are that, while the number of pleas of insanity has increased sharply in the jurisdictions accepting the Durham decision, the percentage of acquittals has not.

It has been attacked as effecting a reduction in the deterrent value of punishment. Many behavioral scientists doubt the validity of the concept that punishment for wrongdoing carries with it any inherent deterrent value. Many sociologists and psychologists argue that deterrency is inculcated into the individual through such agencies as family, society in general, and religion and thus is a feature of the superego which is not vulnerable to the influences of specific statutes.

It has been attacked by the moralists who see it as a contradiction to the concept of free will; this is clearly a twentieth century echo of Bodin's thesis (promulgated as a refutation of Johann Weyer).

Mens Rea and Actus Reus

Most students of law and of psychiatry, however, consider the primary shortcoming of the Durham decision to be the intangible link between act and disease or defect of mind, a relationship which must be such that the former can be clearly established as a consequence of the latter. The law has traditionally exacted fulfillment of the requirements of *mens rea* (state of mind which could lead in a rational fashion to the alleged criminal action) and *actus reus* (the establishment of the fact that a criminal act has been committed) before a person can be indicted for a crime, a step preliminary to prosecution and trial.

The Durham decision—as do all tests of insanity—concerns itself with the nature of the *mens rea,* accepting the causal link between intent and act once an indictment has been entered. It does not ask whether or not the act was a product of the mind of the accused; this has already been asked and answered affirmatively. It asks whether or not the act was a product of the diseased mind of the accused, once the fact has been established that the accused does indeed possess a diseased or defective mind. This so-called disease-product test, first proposed by Judge Doe in 1871 and later adopted by Judge Bazelon and the District of Columbia Circuit Court of Appeals in the 1954 Durham decision, has in fact been rejected by every other court (as of 1961) which has considered it. The reasons for its rejection arise quite clearly and consistently from the fear that accepting it will be a blow to the premise of free will. A prominent jurist has said that all law in western civilization is directed by a strong common sense which assumes the existence of freedom of the will as a working hypothesis in the solution of legal problems.

Concept of "Disease Product"— Carter vs. U. S.

The District of Columbia Circuit Court of Appeals in subsequent decisions tried to clarify the concept of "disease-product" and correct its shortcomings. In Carter vs. the United States,[5] this court said in 1957:

The basic import of the criminal law is punishment for a vicious will which motivates the criminal act. The defendant is not to be found guilty as charged unless it is established beyond a reasonable doubt that when he commits the act, first, that he understood and appreciated that the act was a violation of law; and second, that he had the capacity to exercise his will and to choose not to do it. If, because of some abnormal mental condition, either of these elements is lacking, he cannot be found guilty. To hold

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him guilty the jury must find, beyond a reasonable doubt, both that he understood and appreciated the act charged was a violation of law, and that he possessed the capacity and competence to choose to do it or refrain from doing it.

The Carter decision thus gives new impetus to the cognitive test while emphasizing as well the role of will; yet, it does not restrict psychiatric testimony regarding an alleged mental disease which might interfere with either. Other decisions by this court further modified and molded the Durham decision; these included decisions which explored the diverse manifestations of mental illness, in relation to admissibility in evidence, as well as the disease-product dilemma.

The Durham decision assumed that mental disease can produce criminal acts, and, indeed, psychiatrists as well as jurists are divided on this issue. Roche[6] stated that "the idea that mental illness causes one to commit a crime has an unmistakable lineage from demonology." Szasz[7] said that "the very occurrence of almost any crime today functions as a powerful impetus for the creation of a theory to explain it."

Medical View and Legal View Irreconcilable

It now is plain that the Durham decision did not serve as a panacea for the age-old problem of forensic psychiatry. If neither decisions based on the McNaughton rule, which pay homage to a pathognomonic sign of mental illness, nor those based on the Durham decision, which raise imponderable considerations of free will, solve the dilemma of justly and fairly ascribing criminal responsibility when mental illness is at issue, where then does the solution lie? There are those who argue that the medical view of mental illness and the legal view of insanity will always be irrevocably irreconcilable.

Fundamental Changes Required

The solution would seem to require two quite fundamental changes in the basic philosophy and practice of our judiciary system, sidestepping the issue of semantics altogether.[2]

Determine Guilt & Punishment

The first change is separating the dual functions with which the trial is endowed: namely, determining guilt and levying punishment.

Determine Insanity

The second change, in essence a corollary to the first, is recognizing the impossible responsibility with which a group of 12 laymen is charged: to assimilate, integrate, and weigh the psychiatric evidence in an effort to decide whether the accused is or is not insane.

It would seem that we are expecting too much when we ask these 12 persons to render a medical judgment over which psychiatric experts are in disagreement in any given trial. Promulgating these changes would have the effect then of reserving to the trial judge and jury the responsibility and duty of ascertaining whether the accused did or did not commit the unlawful act as charged. If the trial phase finds the defendant guilty of committing the act, and if insanity is raised by the defense as a mitigating circumstance, then the role of insanity in determining the commission of the act should be decided by a post-trial hearing, after which sentencing or treatment would be undertaken.

Psychiatric testimony would then be removed from an adversary setting and confined to the post-trial phase. Ideally, this testimony would be weighed by a panel of experts, including a jurist, a psychiatrist, and others of professional training in the behavioral sciences. Psychiatric testimony would be based on an objective evaluation of the accused following his trial; sentencing or treatment would be prescribed accordingly after the public sentiment had waned and the demand for retributive punishment attenuated. Finally, the issue of insanity would be pre-empted from the jury forum.

Pre-trial Psychiatric Examination

There have been two recent efforts to alleviate the plight of forensic psychiatry. In

Massachusetts the so-called Briggs law provides for an automatic pre-trial psychiatric examination of all persons who are indicted for a capital crime, of all persons who have been indicted previously, and of all persons who have been previously convicted of a felony.

Mentally Ill Exempt from Trial

The theory of pre-trial evaluation is based on the aim of removing psychiatric testimony from the jury forum. On the basis of such examinations, persons who are mentally ill would be exempt from trial, and a treatment tribunal would advise the court regarding commitment proceedings. In this case, however, the person still would not have had his day in court relative to the charge brought against him and, in the event of recovery, he would be liable for trial and sentencing.

Inability to Appreciate Criminality

The other effort was by the American Law Institute[2] in 1962, which advocated a model penal code which states that "a person is not responsible for criminal conduct if at the time of such conduct as a result of mental disease or defect, he lacks substantial capacity either to appreciate the criminality of his conduct or to conform his conduct to the requirement of the law." To this is appended a caveat to the psychopath: the code specifically excludes antisocial character disorders from the meaning of mental disease or defect.

Legal Treatment of Criminally Insane

The concept of acquittal by reason of insanity brings up the controversial issue of treatment. In some jurisdictions—notably Massachusetts—when the charge from which the defendant has been so acquitted is homicide, the law decrees that the individual be automatically incarcerated in a state hospital for life, the only authority for dismissal being vested in the governor. Many other jurisdictions have incorporated into their penal codes mandatory hospital sentences, and it is not uncommon to find a more lenient penitentiary term prescribed for a given offense than would be the corresponding statutory hospitalization. These statutes suggest that there are hidden overtones of retribution and deterrence dictating the courts' actions and the legislatures' whims which established them. More liberal laws prescribe that release from the hospital of a person acquitted by reason of insanity should be based on the patient's ability to prove, beyond a reasonable doubt, that he will not be dangerous to others within the forseeable future; this proof can be based on the testimony of a hospital physician in a court hearing.

Concern for the rights of the individual should be paramount in instances of mandatory hospitalization. The traditional right of habeas corpus receives special treatment in some states where proceedings leading to habeas corpus make it incumbent on the patient to establish, beyond a reasonable doubt, that the hospital superintendent has acted arbitrarily and capriciously in refusing to certify the patient to district court for discharge. In such actions, this places a far greater burden on the appellant than he must bear in criminal proceedings. Szasz, together with many others, deplored the transformation of mental hospitals into surrogate prisons, and this issue promises to generate considerably more debate in the years ahead.

To make prisons into hospitals, hospitals into better hospitals, and judicial forums into treatment tribunals while preserving the liberty of the individual from further compromise is a Herculean task, the impediments against which are succintly articulated in this paragraph from Zilboorg and Henry.[1]

"It is fundamentally not so much the struggle for the humane recognition of the criminal's psychopathological shortcomings and the insane individual's human needs, as it is a struggle for that enlightenment without which the average man is unable to cease being afraid of the lawbreaker and the lunatic. As long as this deep-seated fear persists, the criminal and the insane are bound to be treated with that harshness and neglect which does not permit public opinion to com-

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prehend that those anti and unsocial manifestations are accidents of life that are painful and at times horrible but never disgusting, reprehensible, or punishable."

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1. Zilboorg, Gregory, and Henry, G. W.: A History of Medical Psychology. New York, W. W. Norton & Company, Inc., 1941, pp. 239 and 413.
2. Glueck, Sheldon: Law and Psychiatry: Cold War or Entente Cordiale? Baltimore, The Johns Hopkins Press, 1962, p. 44.

3-7 May be secured from the author or the reprints.

Papyrus Ebers[*]

For Burns

For burns the ancient Egyptians had a number of remedies, the simplicity of which belied their startling ingredients: the hair of a cat, a portion-of-cake, the head of an electric eel, etc. However, a five-day series of surefire remedies was preferred.

Against Burns: To Use on the First Day

Black amat-juice
Put thereto.

Another on the First Day

Elderberries
uah-corn
Cat's dung
Mix into one in Cake-water and apply thereto.

To Use on the Second Day

Goat's dung
Burn, crush, rub in Yeast-that-is-fermenting, and put thereto.

To Use on the Third Day

Thorns-of-Acanthus, dried
Crush them in cooked durra-corn and Onions, put in Oil, and apply as a plaster.

To Use on the Fourth Day

Wax
Roasted Cow's Fat
Palm-fibres
Make into one in uah-corn, and apply as a plaster.

To Use on the Fifth Day

Onions
Red-lead
Fruit-of-the-am-tree

Crush, rub in Copper-splinters, make into one and apply as a plaster.[**] Should the burn prove too stubborn to yield to such heroic measures, the gods were invoked for reinforcements.

Incantation for a Burn

'O son, Horus! There is Fire in the Land! Water is not there and thou art not there! Bring Water over the River-bank to quench the Fire.' To be spoken over Milk-of-a-Woman-who-has-borne-a-Son.[**]

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[*] See Minnesota Med 48:1468, 1576 and 1694, 1965, and 49:124, 1966.

[**] Bryan, Cyril: The Papyrus Ebers, D. Appleton and Company, New York, 1931, p. 69-71.

Perinatal Mortality Study

Erythroblastosis Fetalis

This was the fourth pregnancy of this 30-year-old Rh negative mother. Her first child was full term and normal. Her second child was born three weeks prematurely and died at age three hours from erythroblastosis fetalis. Her third child was a macerated stillborn at 5½ months' gestation. During the present pregnancy, the mother had one Rh titre determination at 33 weeks of gestation, which was reported as "low titre." Fetal heart tones were present during the mother's prenatal visit at 36 weeks, but were absent when the mother was admitted to the hospital after going into labor at 38 weeks. She delivered a 7 lb., 6 oz. stillborn infant. The size and condition of the placenta was not noted. Autopsy on the infant revealed considerable edema of all extremities, along with hepatosplenomegaly and microscopic changes consistent with the diagnosis of erythroblastosis fetalis. Rh studies on the mother's blood following delivery revealed sensitization to the C and D factors.

Comment

The Perinatal Mortality Study Committee criticizes the care that this mother received, particularly with her past history of delivering a child dying of erythroblastosis fetalis, followed by a delivery of a macerated stillborn. The mother should have had repeat Rh titres during the pregnancy to check for a rising titre; although even a low Rh titre may often be associated with a severely involved erythroblastotic infant. The Rh titre cannot be relied upon to indicate whether or not or how severely the infant may be affected with erythroblastosis. Some hospitals have facilities for amniocentesis, which is performed at 30 to 32 weeks and repeated at 34 to 36 weeks of gestation. Bowman and Pollock[1] present a good review of amniocentesis. Amniocentesis gives a reliable estimate of how severely the infant is affected with erythroblastosis, and whether or not to induce premature labor.

In the present case, even in the absence of amniocentesis, the mother should have had induction of labor at 36 weeks of gestation because of the erythroblastosis in her previous pregnancies.

The Perinatal Mortality Study Committee will continue to study perinatal deaths to find factors which could be favorably controlled, thus improving the care given to mothers and their infants.

Hennepin County Perinatal Mortality Study Committee

Reference

1. Bowman, J. M., and Pollock, J. M.: Amniotic Fluid Spectrophotometry and Early Delivery in the Management of Erythroblastosis Fetalis. Pediatrics 35:815, 1965.

Case 2

The mother of this infant was 21 years old, Rh negative, and this was her fourth pregnancy. Her first infant was normal. Her second pregnancy resulted in twins born six weeks prematurely, both of whom required an exchange transfusion because of erythroblastosis. Both twins lived. The mother's third pregnancy resulted in a jaundiced stillborn at eight months of gestation.

During the present pregnancy, the mother had no Rh titre determinations and no attempt at early induction of labor. At 38 weeks of gestation she had spontaneous labor. Fetal heart tones were not heard during the 11-hour labor. The mother gave

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birth to an eight pound, one ounce extremely edematous infant that had petechiae, particularly over the face. The presentation was left occiput posterior. The infant was given oxygen and made several attempts to breathe but expired at three minutes of age. Cord blood was Rh positive and Coombs positive. No autopsy was done on the infant. The placenta measured 26 by 16 cm. and was consistent with erythroblastosis.

Comment

The Perinatal Mortality Study Committee criticizes the care that this mother received during pregnancy. Reference is made to a recent article in "The New England Journal of Medicine" which criticizes a perinatal death due to erythroblastosis fetalis.[1]

The Committee makes the following criticisms:

1. The mother should have had serial Rh titres done during the pregnancy. Some hospitals also have facilities for amniocentesis[2] which should be done at about 30 weeks of gestation and repeated at 34 weeks of gestation.
2. With the history of erythroblastosis in the second pregnancy, followed by an erythroblastotic stillborn in the third pregnancy, the mother should have had early delivery in her present pregnancy, perhaps as early as the 36th week of gestation. Rh negative blood compatible with the mother's blood should be available before delivery. The blood may be needed for an exchange transfusion immediately after delivery. It is inexcusable not to determine the severity of the disease and attempt to terminate pregnancy early for the mother in this case.

The Committee will continue to study perinatal deaths to elucidate preventable factors. Only by improving the prenatal care of Rh negative sensitized mothers can we as physicians hope to salvage more of the infants resulting from these pregnancies.

Ramsey County Perinatal Mortality Study Committee

References

1. Jewitt, J. F.: Fetal Death Due to Erythroblastosis Fetalis. New Engl J Med 273:663, 1965.
2. Bowman, J. M., and Pollock, J. M.: Amniotic Fluid Spectrophotometry and Early Delivery in the Management of Erythroblastosis Fetalis. Pediatrics 35:815, 1965.

Plutarch (A.D. 46-120) recites a tale: "Once Antigonus was told his son was ill, and went to see him. At the door he met some young beauty. Going in, he sat down by the bed and took his pulse. 'The fever,' said Demetrius, 'has just left me.' 'Oh, yes,' replied the father, 'I met it going out the door.' "

Saul, F. William, M.D.: Pink Pills for Pale People,
Dorrance & Co., Philadelphia, 1949.

New Frontier

Economists have not yet earned the right to be listened to attentively.
— John Maynard Keynes

Economy is going without something you do want in case you should, some day, want something which you probably won't want. — Anthony Hope Hawkins

History of Medicine

Rudolf Ludwig Karl Virchow

(1821-1902)

"Omnis Cellula E Cellula"

Rudolf Virchow's DIE CELLULARPATHOLOGIE was published in 1858,, nearly a century and a decade ago. Yet today this dictum: OMNIS CELLULA E CELLULA remains entirely valid.

Writing in his Archiv in 1877, thirty years after the founding of his periodical, Virchow speaks in retrospect as well as precognition. . . "As a result of daily observation, the heretical thought of the continual reproduction of cells within the individual gradually germinated and grew. These thoughts became the basis of cellular pathology.

What we should have learned, in the period of a generation which lies behind us, is above all the realization that pathology must be an independent science. . . One should remain aware that this emancipation of pathology, this elevation of pathology to the rank of a natural science, requires before all else that pathologists guard their independence, that they permit no strange science to introduce its hypotheses into pathology at will, in order to prevent it from again being pushed back to the position of a mere applied science."[1]

Born in Schivelbin, Pomerania, one of the northeastern German provinces, Virchow was well grounded in ancient and modern languages at an early age. Entering Coeslin Gymnasium at the age of fourteen he pursued Latin, Greek, Hebrew, and Italian. By the time he matriculated at the University of Berlin at the age of eighteen, he was an accomplished linguist. At a result of this early training, Virchow was a skillful glossologist, being a master of exactness in his choice of words and terminology. At the University he developed a deep interest in the basic concepts of natural science. Graduating in 1843, he was appointed assistant prosector at the Charite Hospital, working under Robert Froriep. There . . . "in addition to dissecting dead bodies, he cultivated industriously two studies that in his far seeing judgment were to rejuvenate pathology, microscopic study of tissues and analytical chemistry."[2]

In 1846 he became prosector of the hospital. Soon after this he joined the teaching staff of the University. Associating himself with two outstanding pathologists of the day, Benno Reinhardt and Ludwig Traube, . . . "they did experimental work at that early period on tuberculosis of the lung as influenced by section of the vagus. The remarkable thing about this promising phase of his productive life is not, as Becher* writes, so much that he made original discoveries in leukemia, thrombosis, embolism, and so forth, but rather that he introduced new methods of research, namely, experimental pathologic study."[3] In 1847 Reinhardt and Virchow produced their own journal. "This was a move of outstanding importance. The journal met a hearty reception from the medical profession as filling an obvious need, and has remained the leading journal of pathological anatomy to the present time. With Reinhardt's untimely death it passed into the exclusive editorial control of Virchow and has since been known by the simple abbreviation 'Virchow's Archiv.' "[4]

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*Becher, W.: Rudolf Virchow, Eine biographische Studie, Karger, 1891.

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Another consuming and life-long interest of Virchow, aside from his study of pathology was the study of economic and social problems. In 1848 he was appointed a member of a commission to investigate an epidemic of typhus fever in Silesia. His report of conditions there as he found them revealed deplorable social conditions along with revolutionary recommendations for their correction. The Government in power felt he was too democratic, so he was gradually relieved of his prosectorship at the Charite.

(Continued Next Month)

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3. Bartlett, Willard: Mayo Foundation Lectures on the History of Medicine, A Sketch of Virchow's Life and Time, W. B. Saunders, 1933, p. 463.
4. Long, Esmond R.: A History of Pathology, Williams & Wilkins, 1928, p. 193.

Aneurysms

Aneurysms occur in every part of the body, but especially beside the windpipe, in the formation of the so-called aneurysmal bronchocele. Usually the formation of an aneurysm is through percolation of the blood and air which is contained in the arteries, or by anastomosis of arteries, or by their rupture; the blood and air escape gradually and collect under the skin. Signs which accompany an aneurysm are: a small or large swelling, of uniform color, painless, extremely soft and elastic. It yields to the pressure of the fingers, so as to become almost imperceptible, and then again rapidly swells up.

Such, then, are the signs of the condition; no surgeons, however, will have anything to do with it when it occurs in the throat or the head; for as soon as an aneurysm is opened there takes place a most violent hemorrhage, very difficult to check, and at the same time a great quantity of vital pneuma (spirit) escapes; hence the individual undergoing operation runs the risk of dying on the physician's hands.

In the case, however, of aneurysm in the hollow of the elbow, we proceed thus: we first mark carefully the artery as it leads from above along the inside of the upper arm from the axilla to the elbow, and we make a simple incision along the inside of the arm, three or even four fingers' breadths below the axilla, where the artery mostly becomes palpable. Then gradually laying it bare, we gently strip it and free it from surrounding structures; then, drawing it up with a blunt hook, we apply two strong ligatures of twisted flax, at an interval of the breadth of a thick finger from one another. Tying these very firmly, we sever the artery midway between the ligatures; then, having filled the wound with manna and inserted a drain we apply bandages. Thereafter we incise the swelling in the hollow of the elbow, having no further fear of hemorrhage. After turning out the clots we search for and find the bleeding artery; this we draw out with hooks and ligature it like the former one; then again, filling the wound with manna, we have recourse to the suppurative treatment.

Aetius of Amida, Sixth Century A.D.

When we put ourselves in the hands of a physician, we don't want to detect freckles of gold dust. — Houston Chronicle 8/12/65

Medicine and Religion

Faith in Medicine—Two Forces, One Goal*

Throughout all America there is new recognition of the concept that man is a whole being: that he is physical, spiritual, emotional and social in his total health. It is also widely recognized that a weakness in any one of these four factors of his health can and does militate toward ill health in any one or two or all three of the other factors. All illness is not organic; the parents of the retarded child in some cases are more ill than the child. Moments of shock, fear, hysteria, and grief are moments of serious illness, which can affect the whole being of the patient.

The faith of the individual patient is a vital factor in total health, and he must be treated and cared for within the scope of that faith. There needs to be greater understanding between physicians and all faith groups as to the requirements of those faiths relative to patient care.

The physician recognizes that he treats but God heals. In the treatment and care of the patient, the faith of the patient has much to do with the healing process — the will to live or to die, and this cannot be purchased in a bottle at the drug store.

If man is to find total health, the abundance of life which has been promised to him by his creator, God, then it is essential and necessary that he develop to the fullest extent a perfect body, physically; a perfect mind, mentally; a perfect soul, spiritually; and a perfect life, socially. Whether our illness is physical or spiritual, we realize the need of the physician and the clergyman to associate themselves in concern for this total man.

"The church is primarily concerned with the patient's spiritual welfare and the physician with the patient's physical condition, but all of us are aware of the complexity of the individual and the importance of treating the whole patient," says Doctor Edward H. Rynearson of the Mayo Clinic. Among all the alliances in effect today, none, I believe, will prove more productive and beneficial to human welfare than the alliance of medicine and religion.

We hear the question: to what extreme does the doctor use extraordinary measures to maintain life, in view of the fact that it is his credo to do all in his power to sustain life? And what are "extraordinary measures"? That which was extraordinary ten years ago is ordinary today. Also, to what extent do we maintain the patient as a merely vegetating organism? We are not referring here to euthanasia or mercy killing, for medicine as a profession is opposed to both. The physician and the clergyman need to have dialogue in these areas; they need to discuss this carefully with understanding and compassion, so that the physician can be guided to a correct decision.

The confidence that the average family places in its clergyman and its physician requires that the two consult with each other whenever necessary. From their collective judgment will come the means for providing the most effective care and treatment of the patient as a whole man. This is the new concept.

These then, are the two forces — medicine and religion — operating with one objective, that you and I may receive the finest care and treatment in our illness, knowing full well that illness may be organic, may be spiritual, may be emotional or mental, may be social. This, then, is our goal — total care.

Rev. Dr. Paul B. McCleave**
Chicago, Illinois

The great secret of successful marriage is to treat all the disasters as incidents, and none of the incidents as disasters. — Harold Nicholson

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*Excerpt from presentation at the Minnesota State Medical Association Annual Meeting in Minneapolis, May 17th, 1965.

**Department of Medicine and Religion, American Medical Association.

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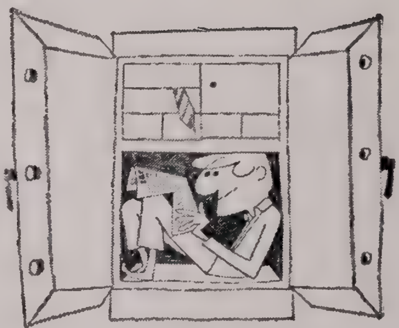

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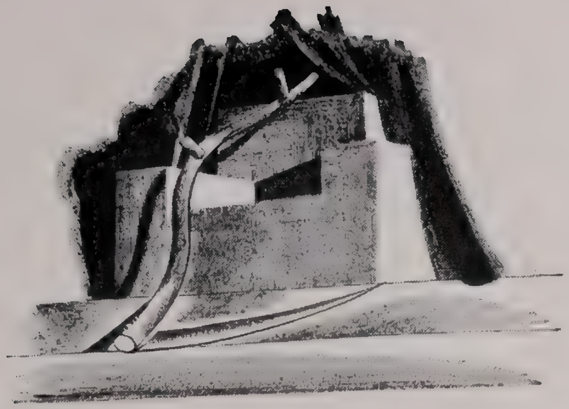

In Memoriam

No man who is fit to live need fear to die. — Fuller

WILLIAM R. LOVELACE, II, M.D.

Dr. William Randolph Lovelace II, 57, president of the Lovelace Foundation, Albuquerque, New Mexico and director of space medicine in the Manned Space Flight Division of the National Aeronautics and Space Administration, was killed, with Mrs. Lovelace, when an airplane which he had chartered crashed in Grizzly Gulch, near Aspen, Colorado, on December 12th. He was born in Springfield, Missouri, and received his degree of doctor of medicine from the Harvard Medical School.

Dr. Lovelace came to Rochester July 1, 1936, as a fellow in surgery of the Mayo Graduate School of Medicine, and was appointed a first assistant in surgery to Dr. Charles W. Mayo in 1939. He became a member of the staff of the Mayo Clinic in 1941. In 1940 with the late Doctors Walter Boothby and Arthur Bulbulian, he was given the Collier Trophy Award for his participation in the studies of the three men, which produced the Boothby-Lovelace-Bulbulian oxygen mask for the use of flyers at extremely high altitudes. In 1943 he made a parachute jump from a height of 40,200 feet to test oxygen equipment. In October to December, 1946, he was on leave of absence from the Mayo Clinic to practice surgery at the Lovelace Clinic in Albuquerque, New Mexico, and thereafter remained with the Lovelace Clinic.

Dr. Lovelace never relinquished his abiding interest in aviation medicine. In 1942 he was appointed director of research and consultant in surgery in the office of the Air Surgeon General, and in 1942 he was president of the Aero Medical Association. From then on, Dr. Lovelace held various offices in space associations and foundations. His awards and citations were many, and among these was the Outstanding Achievement Award from the University of Minnesota in recognition of noted professional attainment which he received in 1964 at the Mayo Centennial.

He was certified as a specialist in surgery by the American Board of Surgery in 1942; he was one of the founders, in 1953, of the sub-board of aviation medicine of the American Board of Preventive Medicine, and had been a fellow of the American College of Surgeons since 1942. He was a member of the board of directors of the Garrett Corporation, and of the Western Surgical Association, Pan-Pacific Surgical Association, the American Medical Association, the Aero Medical Association, the Association of Military Surgeons of the United States, the Institute of the Aeronautical Sciences, Inc., the African Research Foundation, the Space Educational Foundation and the Alumni Association of the Mayo Graduate School of Medicine.

He is survived by three daughters.

OLAF J. HAGEN, M.D.

A long-time leader in Minnesota's medical and educational circles, Dr. Olaf J. Hagen, 93, Moorhead physician, died December 3. He was born in Menomonie, Wisconsin, and received his degree in medicine from the University of Minnesota Medical School.

Among his honors was an outstanding achievement award from the University of Minnesota board of regents, to which he was named in 1931. He founded the Fargo Clinic, and succeeded the late Dr. Charles Mayo as president of the Minnesota Public Health Association.

He was a member of the American Medical Association and the Clay-Becker County Medical Society, and a 50 Club and life member of the Minnesota State Medical Association.

He is survived by a daughter and a son.

CARL B. DRAKE, M.D.

Dr. Carl B. Drake, 79, long-time officer of the Minnesota State Medical Association, died December 9, in his sleep. A life-long resident of St. Paul, he was a graduate of the University of Minnesota Medical School.

Continued

For thirty-four years, he served as school physician for the St. Paul Academy, was on the Ancker Hospital medical staff for forty years, and a member of the clinical faculty of the University of Minnesota.

Dr. Drake was a past secretary of the Minnesota State Medical Association. He was elected president-elect of the Minnesota State Medical Association but was prevented by illness from serving in this capacity. Dr. Drake was vice president and president of the Ramsey County Medical Society. He was editor of *Minnesota Medicine* from 1919 to 1953 and recipient of the Minnesota State Medical Association's distinguished service award. He was also a member of the American Medical Association and a 50 Club member of the Minnesota State Medical Association.

He is survived by his wife and three sons, one of whom is Dr. Emerson H. Drake of Portland, Maine.

CARL G. ARVIDSON, M.D.

Dr. Carl Gustav Arvidson, 74, Minneapolis physician, died December 12th. He received his medical degree from the University of Minnesota, and headed the Venereal Disease Clinic for Women at General Hospital from 1920 to 1925. He was a supervisor in venereal disease diagnosis at Sauk Centre Home School for Girls and at state institutions in St. Cloud, Shakopee and Stillwater.

Dr. Arvidson was on the staff at Swedish Hospital and belonged to the American Institute of Swedish Arts, Literature and Science. He was a member of the American Medical Association, Hennepin County Medical Society and a life member of the Minnesota State Medical Association.

He is survived by his wife and a daughter.

HARRY C. JENSEN, M.D.

Dr. Harry C. Jensen, 70, Minneapolis general practitioner, died January 2. He was born in Hutchinson, Minnesota, and obtained his medical degree at the University of Minnesota Medical School.

He was a staff member of the Deaconess Hospital, associate member of the Minnesota State Medical Association, member of the American Medical Association, member of the Hennepin County Medical Society and owner of the Edina Medical Center.

He is survived by his wife and a daughter. Dr. Verner M. Jensen of Morningside is his brother.

ROGER L. J. KENNEDY, M.D.

Dr. Roger L. J. Kennedy, 68, widely-known specialist in diseases of children and former head of the Section of Pediatrics of the Mayo Clinic, died January 14. He was born in St. Paul and received his degree of medicine from the University of Minnesota.

Dr. Kennedy was president of the Minnesota State Medical Association in 1952 and had served as president of the American Pediatrics Society. He was a former president and secretary and treasurer of the Northwestern Pediatric Society, a member of the editorial board of the *American Journal of Diseases of Children* from 1951 to 1961, a member of the council of the Minnesota State Medical Association from 1947 to 1951, had been a member of the House of Delegates of the American Medical Association, and was president of the American Academy of Pediatrics in 1953. In 1951 Pope Pius XII conferred upon him the order of Knight of St. Gregory the Great.

A fellow of the American Academy of Pediatrics, Dr. Kennedy was also a member of the Society for Pediatric Research, the Minnesota State Medical Association, the Southern Minnesota Medical Association, the Zumbro Valley Medical Society and the Alumni Association of the Mayo Graduate School of Medicine.

He is survived by his wife, a daughter and three sons. One of his sons, Dr. James Arthur, is engaged in medical research in the U. S. Air Force and another son, Michael, is a medical student at the University of Minnesota.

ARCHIBALD O. OLSON, M.D.

Dr. Archibald Olson, 65, prominent Duluth ophthalmologist, died January 6. Born in Mandan, North Dakota, Dr. Olson graduated from Rush Medical School in 1929.

He was a past president of the Minnesota Academy of Ophthalmology, a member of the American Academy of Ophthalmology, the St. Louis County Medical Society, the Minnesota State Medical Association, and the American Medical Association. He was a past chief-of-staff at St. Luke's Hospital and a member of the staff at St. Mary's and Miller Memorial Hospitals.

He is survived by his wife, a son and two daughters.

The surgeon should be learned, skilled, ingenious, and of good morals. Be bold in things that are sure, cautious in dangers; avoid evil cures and practices; be gracious to the sick, obliging to his colleagues, wise in his predictions. Be chaste, sober, pitiful, and merciful; not covetous nor extortionate of money; but let the recompense be moderate, according to the work, the means of the sick, the character of the issue or event, and its dignity. — Guy de Chauliac (circa 1295-1370)

Medical Economics

AMA Delegates Pass "Billing for Medical Fees" Resolution

Delegates attending the American Medical Association Clinical meeting in Philadelphia heard considerable discussion regarding the direct billing of patients as opposed to the acceptance of assignments for payment by a third party. In lieu of several resolutions, the delegates adopted a substitute resolution which included eight statements on fees charged by physicians for medical services. These are:

"1. The intimate relationship between physician and patient is served best without the interposition of any third-party carrier, whether in the area of diagnosis and treatment or the payment for these services.

"2. It is the patient's responsibility to deal with third-party carriers in the area of financial assistance provided that the physician is at all-times mindful of his obligations to the patient under Section 1 of the Principles of Medical Ethics.

"3. The physician-patient relationship is served best when there is an advance understanding regarding the payment of fees and the physician bills the patient directly for services rendered. However, the physician is ethically free to choose in each case the manner in which he is to be compensated, based upon the exercise of his independent judgment.

"4. The American Medical Association does not approve of any program which may directly or indirectly promote the charging of excessive fees or which interferes with the physician's right to charge fees commensurate with the services he renders.

"5. The American Medical Association opposes any program of dictation, interference, or coercion, whether direct or indirect, affecting the freedom of choice of the physician to determine for himself the extent and manner of participation or financial arrangement under which he shall provide medical care to patients under Public Law 89-97, or other third-party plans.

"6. It should be remembered that insurance does not create any new wealth. It merely assists in conservation. Insurance may conserve the ability of an insured person to fulfill his normal financial obligations. It does not enhance his ability to discharge added responsibilities if they are in the form of increased fees. To use insurance as an excuse to revise professional fees upward is but to contribute to the defeat of its purpose. If these indisputable and self-evident facts are not embraced by the entire membership of the profession, then it will have dealt irreparable harm to the whole movement. Also, any such failure might give impetus to whatever demand now exists for forcing rigid benefit schedules on the professional. (The

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foregoing is from a report of the Council on Medical Service to the House of Delegates at the Clinical Meeting in 1954).

"7. The charging of an excessive fee is unethical and is contrary to Section 7 of the Principles of Medical Ethics. The physician's fee should be commensurate with the services rendered and the patient's ability to pay. (The foregoing is from a report of the Judicial Council which was approved by the House of Delegates at the Clinical Meeting in 1960).

"8. It is not contrary to conscience for the physician to consider the patient's ability to pay if he fixes his particular fee within reasonable limits. In matters relating to fees, the physician should try, to the best of his ability, to insure justice to the patient and himself and respect for his profession. (The foregoing is from an opinion of the Judicial Council in 1958)."

AMA Membership Dues Increase Voted

A $25-a-year increase in membership dues, effective Jan. 1, 1967, was endorsed by the AMA House of Delegates in Philadelphia when it was informed by the Board that additional income will be needed by then to avoid deficit spending.

The increase, to $70 a year for the AMA's 165,000 dues-paying members, will go before the House for final action at the 1966 Annual Convention, because AMA Bylaws state that annual dues may be prescribed by the House only for the ensuing calendar year.

Board Chairman Percy E. Hopkins, M.D. told the House that "during 1964 and 1965, the AMA will have incurred an operating deficit of more than 1 million dollars." The budget for 1966, he said, is now narrowly in balance.

The 1966 budget calls for spending some 27.6 million dollars, Doctor Hopkins reported, including almost 10½ million dollars on scientific programs, 5 million on health education and other medical service programs, more than 1 million to maintain physician records, and another million in the communication's program. Travel and meeting costs will exceed 2 million dollars.

"In a society," Doctor Hopkins said, "which has adopted inflation as a national policy and in which our system of medical care has become a pawn of politicians, it is not realistic to expect that we can limit tomorrow's programs to yesterday's income. Already demands are mounting from medical societies and physicians for a stronger and more effective AMA. These needs must be met, and they must be adequately financed."

Doctor Hopkins said that AMA's income in 1960 was just under 16 million dollars, while in 1966 it will exceed 27 million, an increase of 11 million. "This represents increases of 3.9 million dollars from membership dues, 4.3 million in advertising revenue, and 2.8 million from other sources.

"During this same period," he stated, "the challenges thrust upon the Association required even greater expenditures — from 15.7 million dollars in 1960 to a need for 27.6 in 1966."

In support of the dues increase, the House noted that AMA's dues-paying members provide less than 30 per cent of the Association's income.

Life is compatible with any disease, provided the bowels remain open; any kind of pain, provided the heart remains unaffected; any kind of uneasiness, provided the head is not attacked; all manner of evils, except it be a bad woman. — The Talmud

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Classified advertising rates are twenty (20) cents a word; minimum monthly charge $5.00; key number, fifty (50) cents additional.

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TWO G.P.'s NEEDED — Northern Minnesota county seat. New hospital, office space available, two other physicians in town, anesthetist on hospital staff, good schools, all churches, excellent hunting and fishing, housing available. Full details upon request. Contact: Administrator, Roseau Area Hospital, Roseau, Minnesota.

PART TIME INTERNIST OR GENERAL PRACTITIONER. Good compensation — Midway Area. Alfred F. Anderegg, M.D.; 2500 Como Avenue, St. Paul, Minnesota.

WANTED: Board Certified or eligible internist to associate with group in large, active practice in Minneapolis. Group consists of Surgeon, Obstetrician, Pediatrician and Internist maintaining downtown and suburban offices. Partnership in mind. Contact: Jesse J. Barron, M.D., 1127 Medical Arts Building, Minneapolis, Minnesota 55402, FEderal 2-8259.

OLD, WELL ESTABLISHED multi-specialty group of 23 doctors in Midwestern city has opening for board certified or eligible specialists as follows: orthopedic surgeon, internist, pediatrician, otolaryngologist. All departments established and growing. Well-equipped clinic and excellent hospital facilities in community. Attractive financial plan leading to full partnership. Include curriculum vitae. Full expenses paid for applicants invited for interview. Write: MINNESOTA MEDICINE — 337; 496 Lowry Medical Arts Building, St. Paul 55102.

BUSY, GROWING aggressive 3-man partnership in Northwest Wisconsin serving a trade area of 15,000 needs a well-trained recent graduate with fulfilled military obligations to associate immediately on excellent salary, with partnership in 1 year if mutually agreeable. Modern 15 room air conditioned brick clinic building is being doubled in size this year. 32 bed hospital and new 42 bed nursing home one minute from clinic. New 1500 student consolidated school. Excellent hunting, fishing and outdoor sport facilities in immediate area. Contact: MINNESOTA MEDICINE — 317; 496 Lowry Medical Arts Building, St. Paul 55102.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with early partnership. Write: MINNESOTA MEDICINE — 289; 496 Lowry Medical Arts Building; St. Paul, 55102.

WANTED: Generalist to associate with two man partnership in Northern Minnesota. Community has a thirty-seven bed hospital, X ray and laboratory technicians and nurse anesthetist. Good hunting and fishing. Adequate salary and time off. Contact: A. G. Janecky, M.D., Baudette Clinic, Baudette, Minnesota.

OFFICE SPACE now available in busy Bloomington. 713 square feet of new space in building with busy group of G.P.'s, dentist and suburban OB-GYN office. Ideal for ophthalmology, ENT or pediatrics. 8040 Penn Avenue South. 888-9211.

WANTED: one or two general practitioners. Excellent clinic and hospital facilities. Rural practice established 18 years. Salary open, partnership if compatible. Lloyd H. Klefstad, M.D., Greenbush, Minnesota.

SACRED HEART, MINNESOTA, doctorless since 1961, wants general practitioner. Population 700, accredited hospital 10 miles away. Write: Rev. Robert Bardy, Phone 765-2547, Sacred Heart, Minnesota.

GENERAL PRACTITIONER WANTED: to associate with physician-surgeon in Owatonna, a Southern Minnesota community, 25,000 population. Clinic building three years old; with five large treatment rooms, lab.; x ray; central supply; two doctors' offices; pharmacy; and business offices. Located next door to 85-bed city hospital. Good opportunity for partnership. Contact: O. W. Roberts, M.D.; 920 South Cedar Street; Owatonna, Minnesota. Phone 451-4630.

LOCUM TENENS wanted for general practice in St. Paul from mid-February through March, 1966. Write: MINNESOTA MEDICINE — 328; 496 Lowry Medical Arts Building, St. Paul 55102.

MEDICAL ART. Drawings, charts and lettering for publication, slide lectures, movies, exhibits and television. Also three dimensional models. Al Hage — 339-1012, Minneapolis.

WANTED — Internist, board certified or qualified, to associate with two board certified internists. Ten man multi-specialty group. (Lenont Peterson Clinic, Virginia, Minnesota) — Heart of the expanding taconite industry.

FOR RENT: Successful medical building. Will help doctor or group of doctors get started in proven location in Northwest Suburban Minneapolis, 36th and Noble near two hospitals. Call or write Noble Drug, 4705 36th Avenue North, Minneapolis 22. Ju 8-9449.

WANTED: young general practitioner to join six-man group consisting of 4 GPs, a general surgeon, and radiologist. College town of 5,500, 30 miles from Twin Cities. Also need LOCUM TENENS in general practice. Contact: Ed Jenkins, Mgr., River Falls Medical Clinic, River Falls, Wisc. Phone 425-5322.

WANTED: Immediate opening for young GP in an established medical corporation. Three man G.P. group located in rapid-growing North Suburban Metropolitan Area. 15 minutes from loop and large educational center. New clinic. New 150-bed hospital. Salary open, fringe benefits. Fridley Medical Center, P.A., 203 Mississippi Street, Minneapolis, Minnesota 560-2950.

FOUR STAFF ADDITIONS to Southern California Group of 24 physicians. Internist with chest subspecialty, ophthalmologist, otolaryngologist, general practitioner. Partnership possibility after first year. Administrator, Gallatin Medical Group, 10720 S. Paramount Blvd., Downey, Calif.

WANTED: Young internist and pediatrician, board certified or eligible, to join 6-man group consisting of 4 GP's, a general surgeon, and a radiologist.

College town of 5,500 only 30 miles from Twin Cities. Salary open with early partnership opportunity. Write or call collect: Ed Jenkins, Mgr., River Falls Medical Clinic, River Falls, Wisc., phone 425-5322.

EXCELLENT and immediate opening for one or two physicians. 17-bed fully-equipped municipal hospital with lab and x-ray facilities. Also private 40 bed nursing home. Complete clinic, including equipment, available for rent. Doctor owner retiring because of ill health. No investment needed. Prosperous agricultural community. Opportunity for rewarding lifetime practice. Phone 669-4421 collect, Clarkfield, Minnesota Hospital.

PSYCHIATRIC RESIDENCIES, positions available July 1966. Fully approved, balanced didactic and clinical experiences. Five-year career program: $8,895, $10,294, $12,048, $15,368, $16,203; NIMH general practitioner stipends $12,000 annually for three years in Michigan's water winter wonderland. Paul E. Kauffman, Ph.D., Director of Resident Training, Traverse City State Hospital, Traverse City, Michigan. An equal opportunity employer.

WANTED: General practitioner able to do surgery. Present physician wanting to "semi-retire." Good community, prosperous farming. Good schools and churches. New hospital and clinic buildings. Contact: Warren Clinic, P.O. Box 107, Warren, Minnesota 56762.

WANTED: Young G.P. for rural practice partnership. No initial investment. Previous partner and well-equipped for dual practice. Good hospital — 12 miles and large medical center 30 miles on four lane highway. Small town in stable farming community, resort area, hunting and fishing, good school system. Contact: A. S. Midthune, M.D., Lake Park, Minnesota.

CHIEF OF PSYCHIATRIC SUPERVISORY STAFF needed to help with clinical supervision and teaching in expanding (18 Resident Physicians) fully-approved residence training program. Ideal living in active community in the heart of Michigan's Water-Winter Wonderland. Newly established position requires board certification in psychiatry and additional experience in clinical supervision. Salary range depending upon qualifications, $17,383 to $21,339 with liberal Michigan civil service benefits. Contact Arthur F. Dundon, M.D., Clinical Director, Traverse City State Hospital, Traverse City, Michigan. An equal opportunity employer.

GENERALIST NEEDED. Death of associate in three-man group in general practice in White Bear Lake, Minnesota, requires immediate replacement. Salary with advancement to partnership negotiable. Excellent opportunity for young man in an established practice of young men (under 38 years old). New building in suburban area of St. Paul. Locum tenens also considered. Call or write: A. J. Rushay, M.D. or T. G. Briggs, M.D., 777-1341.

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WANTED: INTERNIST to locate at Apache Plaza Medical Complex in the heart of the N.E. Minneapolis, N.W. St. Paul suburban area. No internist currently practicing within 3 miles of the Medical Complex, an area encompassing 100,000 people. Offices can be ready for occupancy by fall, 1966. For information contact: Apache Corporation, 1800 Foshay Tower, Minneapolis, 55402, phone 612-339-7781.

URGENT need for general practitioner to associate in important industrial and extensive private practice in Northern Minnesota's beautiful Arrowhead country. Excellent 24-hour clinic with full facilities including x-ray, lab., surgical suite. Five-member staff of technicians and nurses. Newly established and fast-growing community serving area of 7,000 with four new schools, many churches, and good hunting, fishing, camping on Lake Superior's North Shore. Liberal fringe benefits. Attractive financial arrangements. Wire or airmail reply to Silver Bay Emergency Hospital and Clinic, P.O. Box 70, Silver Bay, Minnesota. Telephone 226-4461, extension 33, area code 218.

GENERAL PRACTITIONER — MINNESOTA STATE PRISON. Serve as Medical Director of 50-bed hospital with staff of registered nurses and laboratory technician. Surgical resident provided by University of Minnesota. Consultant service in various specialties also available. Residence suitable for family, furnished free-of-charge. Minnesota Civil Service Position. Contact: Mrs. Barbara Sundquist, Box 55, Stillwater, Minnesota 55082 — Telephone 439-1910, Ext. 320.

EXISTENTIAL PRINCIPLES of understanding and treating the patient are employed in supplementation of traditional dynamic methods at our 600 bed hospital. Position as first year resident in Psychiatry beginning July 1, 1966 now available. We offer an intensive didactic and clinical teaching program directed towards board certification. Stipend $11,400 yearly. Will have to be eligible for State licensure. NIMH grants of $12,000 per annum for general practitioners or physicians with at least four years of experience in other than psychiatry. Write: W. C. Brinegar, M.D., Mental Health Institute, Cherokee, Iowa.

UNOPPOSED GENERAL PRACTICE — city 1,850, farming area, southern Minnesota. Hard surface streets, excellent school system, churches, etc. Reason for leaving — specialization. Write: MINNESOTA MEDICINE — 338, 496 Lowry Medical Arts Building, St. Paul 55102.

SOUTHDALE MEDICAL BUILDING — share space with medical specialist. Very convenient to transportation and new hospital next door. Call 920-4161.

FOR SALE: Mattern X-ray unit. 100 K.V. 60ma. Good for chest and extremity work. Also examining table, instrument cabinet, E.K.G. and other equipment. Contact L. A. Whitesell, Jr., M.D. 207 South First St., Buffalo, Minnesota 55313.

Continued to page 372.

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Meetings and Announcements

The pain of dispute exceeds, by much, its utility. All disputation makes the mind deaf, and when people are deaf I am dumb. — Joubert

FEBRUARY

Minnesota Academy of Medicine meeting, February 9, Town & Country Club, St. Paul, 6:30 p.m.

St. Louis County Medical Society Executive Committee Meeting, February 10, 6:00 p.m., St. Luke's Hospital, Duluth. Business Meeting at 8:00 p.m.

Twin City Urological Society Meeting, February 18, Town and Country Club, 6:00 p.m., St. Paul.

Ramsey County Medical Society Meeting, February 28, 1500 Lowry Medical Arts Building, St. Paul, 8:00, p.m.

Sioux Valley Medical Association meeting, February 24 and 25, Sheraton-Warrior Motor Inn, Sioux City, Iowa. Contact: D. M. Youngblade, M.D.; 2417 Pierce Street, Sioux City, Iowa.

American College of Physicians postgraduate course on "Cancer for the Internist," February 21-25, Presbyterian-St.Luke's Hospital, 1753 West Congress Parkway, Chicago. Contact the College at 4200 Pine Street, Philadelphia.

American College of Physicians regional meeting for internists, February 5, Springfield, Hotel St. Nicholas. Contact: Chauncey C. Maher, Jr., M.D., Myers Building, Springfield, Illinois 62701.

American Academy of Allergy postgraduate program on antibodies, February 19-23, Americana Hotel, New York. Contact: American Academy of Allergy, 7356 N. Milwaukee St., Milwaukee, Wisc. 53202

MARCH

Minnesota Society of Anesthesiologists annual business meeting, March 11, Minneapolis. Plans to be announced. Contact: V. S. Lawrence, M.D. 330-3997.

Department of Otolaryngology of the University of Illinois postgraduate course in laryngology and bronchoesophagology, March 21-April 2. Write: College of Medicine, University of Illinois, Post-office Box 6998, Chicago.

American Medical Association Air Pollution Medical Research Conference, Los Angeles, Ambassador Hotel, March 2-4. Contact AMA Office.

St. Louis County Medical Society meeting March 10, 8:00 p.m. St. Mary's Hospital, Duluth. Executive Committee Meeting at 6:00 p.m.

Twin City Urological Society Meeting, March 18, 6:00 p.m., Town and Country Club, St. Paul.

Ramsey County Medical Society Meeting, March 28, 8:00 p.m., 1500 Lowry Medical Arts Building, St. Paul.

Hennepin County Medical Society meeting, March 7, 6:00 p.m., Pick-Nicollet Hotel, Minneapolis.

Hennepin County Psychiatric Society meeting to be held in connection with the Hennepin County Medical Society meeting.

Minnesota Academy of Medicine meeting, March 9, 6:30 p.m., Town and Country Club, St. Paul.

ANNOUNCEMENTS

Dr. Birger Strandell, a member of the faculty of the Caroline Institute, Stockholm, and editor of ACTA MEDICA SCANDINAVICA, will lecture on "Linnaeus" at Rochester, May 10, 1966. The lecture, sponsored by the Mayo Foundation chapter of Sigma XI, will be held a day before the opening of the annual meeting of the American Association for the History of Medicine. Contact: Thomas E. Keys, 200 First Street Southwest, Rochester, Minnesota.

* * *

The twenty-ninth annual meeting of The New Orleans Graduate Medical Assembly will be held March 7, 8, 9 and 10, 1966, headquarters at The Roosevelt Hotel. Presentations will be of interest to both specialists and general practitioners. This program is acceptable for twenty-nine (29) accredited hours by the American Academy of General Practice, Write Secretary, New Orleans Graduate Medical Assembly, 1430 Tulane Avenue, Room 1528, New Orleans, Louisiana 70112.

* * *

The William Osler Medal of the American Association for the history of medicine is awarded for the best unpublished essay on a medico-historical subject written by a medical student. Contact: William Beatty, 303 East Chicago Avenue, Chicago.

* * *

Mayo Clinic and Mayo Foundation clinical reviews, March 28-30 and April 4-6, Mayo Civic Auditorium, Rochester, Minnesota. Limited attendance. Contact: M. G. Brataas, Mayo Clinic, Rochester.

Continued from page 369.

WANTED AT ONCE — a general practitioner — present physician retiring after 39 years. Opportunity to take over well-established practice with no obligation. Office space for rent and equipment available. Accredited hospital. Full details upon request. Write C. L. Sheedy, M.D., 205 Second Avenue N. W., Austin.

WANTED AT ONCE — a general practitioner — present physician retiring after 29 years. Opportunity to take over established practice with no obligation. Office space for rent and equipment available. New and accredited community hospital. Full details upon request. Write: Albert J. Emond, M.D., 720 Third Street, Farmington.

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OTOLARYNGOLOGIST TO join long established group with possibility of partnership in mid-west area. All instrumentation for entire ear, nose and throat available including the operating microscope. Write: MINNESOTA MEDICINE — 339, 496 Lowry Medical Arts Building, St. Paul 55102.

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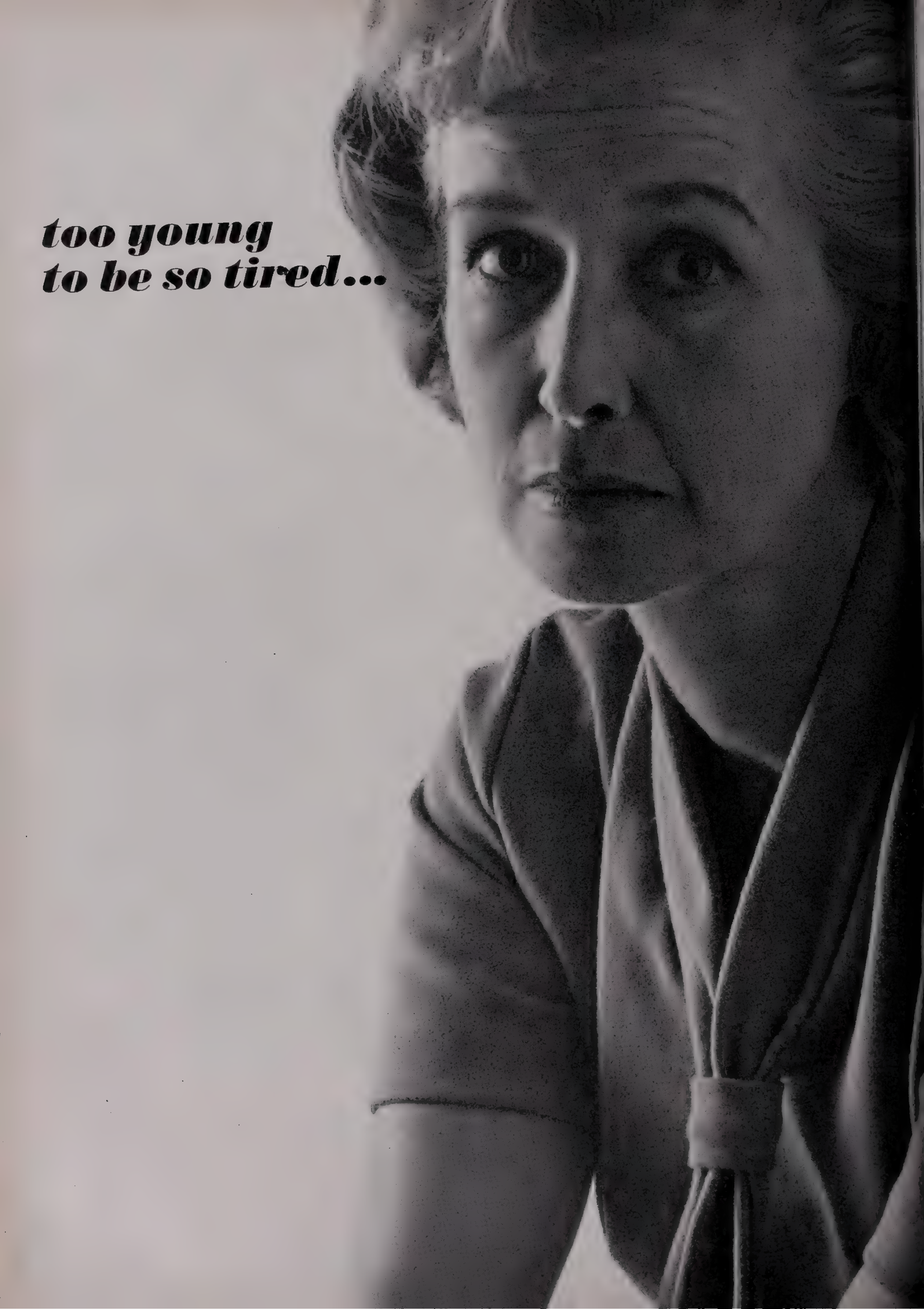
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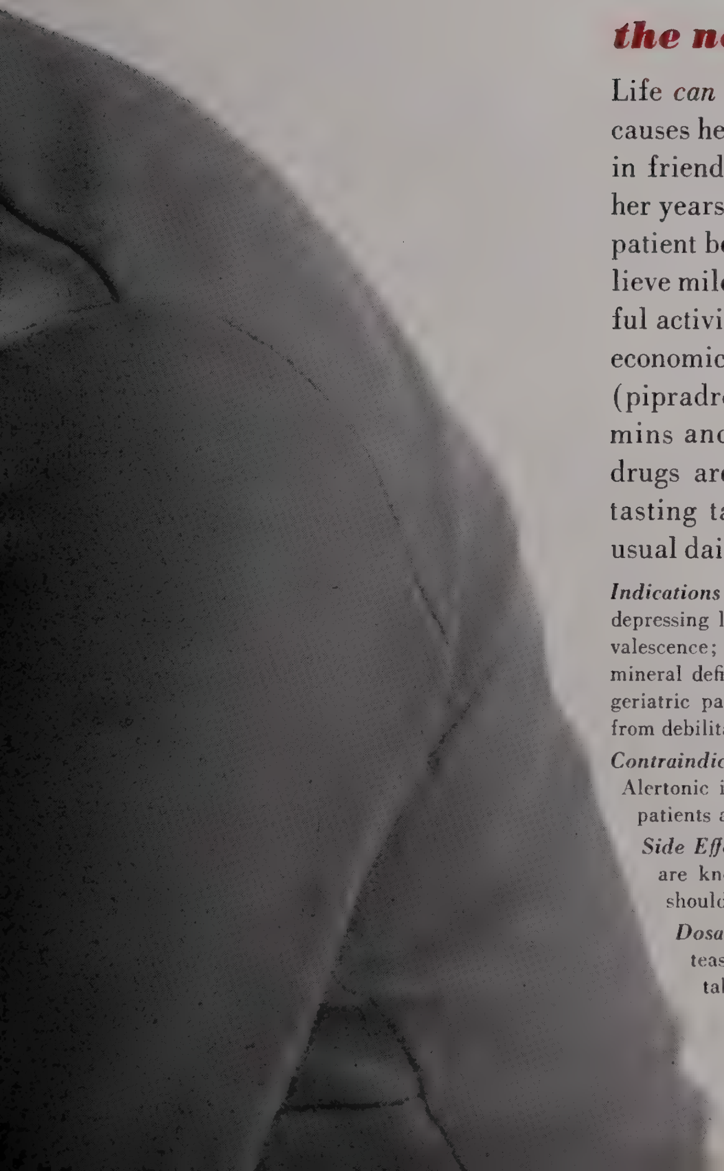

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Use with caution in lower than usual doses in cases with renal impairment to avoid accumulation of tetracycline and possible liver toxicity. If therapy is prolonged under such circumstances, tetracycline serum levels may be advisable. In long term therapy or with intensive treatment or in known or suspected renal dysfunction, periodic laboratory evaluation of the hematopoietic, renal and hepatic systems should be done. Formation of an apparently harmless calcium complex with tetracycline in any bone forming tissue may occur. Use of tetracycline during tooth development (3rd trimester of pregnancy, infancy and early childhood) may cause discoloration of the teeth. Reversible increased intracranial pressure due to an unknown mechanism has been observed occasionally in infants receiving tetracycline. Glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis and definite allergic reactions occur rarely. Severe anaphylactoid reactions have been reported as due to triacetyloleandomycin. Photosensitivity and photoallergic reactions (due to the tetracycline) occur rarely. Medication should be discontinued when evidence of significant adverse side effects or reaction is present. Patients should be carefully observed for evidence of overgrowth of nonsusceptible organisms including fungi, which occurs occasionally, and which indicates this drug should be discontinued and appropriate therapy instituted. Steps should be taken to avoid masking syphilis when treating gonorrhea.

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Precautions: *Meprobamate*—Careful supervision of dose and amounts prescribed is advised. Consider possibility of dependence, particularly in patients with history of drug or alcohol addiction; withdraw gradually after use for weeks or months at excessive dosage. Abrupt withdrawal may precipitate recurrence of preexisting symptoms, or withdrawal reactions including, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, the dose should be reduced and operation of motor vehicles or machinery or other activity requiring alertness should be avoided if these symptoms are present. Effects of excessive alcohol may possibly be increased by meprobamate. Grand mal seizures may be precipitated in persons suffering from both grand and petit mal. Prescribe cautiously and in small quantities to patients with suicidal tendencies.

Side effects: Side effects associated with recommended doses of 'Deprol' have been infrequent and usually easily controlled. These have included drowsiness and occasional dizziness, headache, infrequent skin rash, dryness of mouth, gastrointestinal symptoms, paresthesias, rare instances of syncope, and one case each of severe nervousness, loss of power of concentration, and withdrawal reaction (status epilepticus) after sudden discontinuation of excessive dosage.

Benactyzine hydrochloride—Benactyzine hydrochloride, particularly in high dosage, may produce dizziness, thought-blocking, a sense of depersonalization, aggravation of anxiety or disturbance of sleep patterns, and a subjective feeling of muscle relaxation, as well as anticholinergic effects such as blurred vision, dryness of mouth, or failure of visual accommodation. Other reported side effects have included gastric distress, allergic response, ataxia, and euphoria.

Meprobamate—Drowsiness may occur and, rarely, ataxia, usually controlled by decreasing the dose. Allergic or idiosyncratic reactions are rare, generally developing after one to four doses. Mild reactions are characterized by an urticarial or erythematous, maculopapular rash. Acute nonthrombocytopenic purpura with peripheral edema and fever, transient leukopenia, and a single case of fatal bullous dermatitis after administration of meprobamate and prednisolone have been reported. More severe and very rare cases of hypersensitivity may produce fever, chills, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, anaphylaxis, stomatitis and proctitis. Treatment should be symptomatic in such cases, and the drug should not be reinstituted. Isolated cases of agranulocytosis, thrombocytopenic purpura, and a single fatal instance of aplastic anemia have been reported, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity has been reported, usually after excessive meprobamate dosage. Suicidal attempts may produce lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

Dosage: Usual starting dose, one tablet three or four times daily. May be increased gradually to six tablets daily and gradually reduced to maintenance levels upon establishment of relief. Doses above six tablets daily are not recommended even though higher doses have been used by some clinicians to control depression and in chronic psychotic patients.

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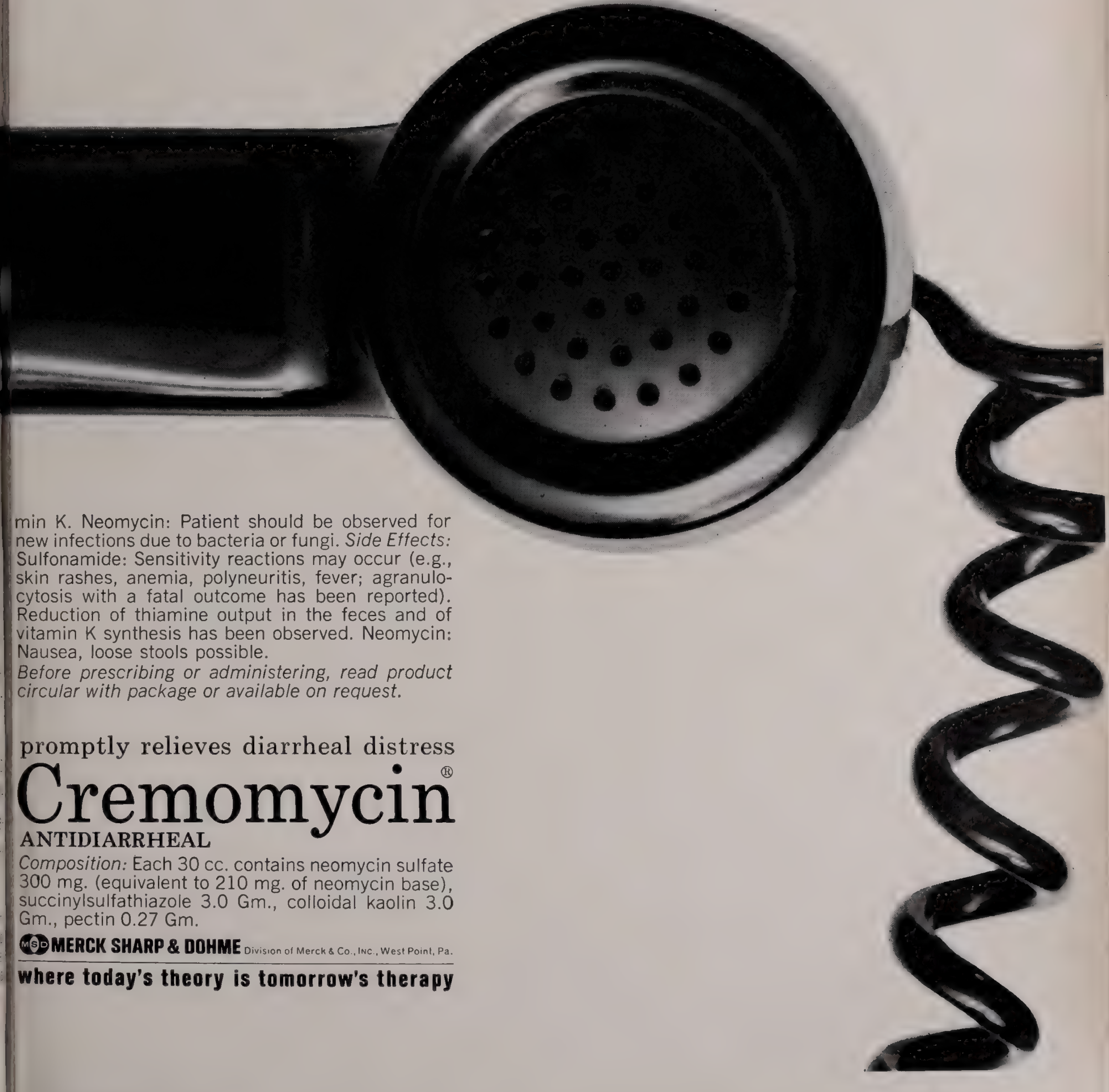

min K. Neomycin: Patient should be observed for new infections due to bacteria or fungi. *Side Effects:* Sulfonamide: Sensitivity reactions may occur (e.g., skin rashes, anemia, polyneuritis, fever; agranulocytosis with a fatal outcome has been reported). Reduction of thiamine output in the feces and of vitamin K synthesis has been observed. Neomycin: Nausea, loose stools possible.
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Minnesota Medicine at a Glance

Tuberculosis and Human Bone Marrow — Schleicher Page 221

The knowledge that tubercles are found only in "marrow units" has made it possible to demonstrate the tubercle bacillus from the bone marrow in individuals suffering with otherwise indefinitely proven tuberculosis. This is possible when meticulous technique is carried out. Separation of the marrow units from the blood and free fat portion of the sample has been found to be important. Though the sternum is the preferred site from which to take the biopsy, the manubrium and the tibia can be used in younger children.

Arteriovenous Fistula — Naffah et al. Page 227

Arteriovenous fistula involving the renal vessels is relatively uncommon, but it may occur as a result of injury or it may be congenital. It is clinically manifest by fatigue, abdominal pain, a palpable mass, flank pain with shock, peripheral edema, fever, renal colic, headache, dyspnea, and hematuria. After an intravenous pyelogram shows some abnormality in the involved kidney, an aortogram can be made to confirm the diagnosis. This condition is amenable to surgical treatment, as has been indicated in the case report.

Sulfonamide-Resistant Neisseria Meningitidis — Walker & Strom Page 232

In some instances children with clinical meningitis can be found harboring sulfonamide-resistant Neisseria meningitidis which is resistant to the usual treatment with sulfonamide. In those instances it should be advantageous to realize that an effective means of determining sensitivity with a modified Wilson tube dilution technique is available, in order that these infants can be more advantageously treated with penicillin and sulfisoxazole.

Scintillation Camera for Brain Pathology — Loken et al. Page 237

The use of large amounts of radioactive material for the purpose of diagnostic scanning is sometimes contraindicated. By using the short-lived radioactive materials in which the half-life is about six hours, this hazard can be eliminated. Loken et al. have used a polaroid camera and the short-lived 99 m-TC radioactive material, and have found that the period of exposure is considerably diminished, thereby making the clinical application of this technique more valuable.

Vein Stripping in Pregnancy — Quattlebaum and Hodgson Page 245

Quattlebaum and Hodgson have made an extensive follow-up study of vein surgery in the pregnant woman and have observed that the final results are as favorable in the pregnant woman as in the nonpregnant patient. They recommend against the stripping of varicose veins during pregnancy except between the fourth and the seventh month of pregnancy, on the basis that to do so in the first trimester and during the last two months of pregnancy may disturb the pregnancy. The technique of vein-stripping is no different in the pregnant woman than it is in the non-pregnant.

Idiopathic Hypertrophic Subaortic Stenosis — Nydahl et al. Page 248

The authors review the pertinent physical, electrocardiographic, roentgenographic, and cardiac catheterization data of the lesion, idiopathic hypertrophic aortic stenosis. Three patients with this problem are described. Each patient had dyspnea, angina, left ventricular enlargement, and a systolic precordial murmur. Electrocardiographic and vectorcardiographic tracings substantiated the left ventricular changes as demonstrated by cinefluoroscopy and selective left ventriculogram. The ventriculogram also demonstrated the change in the septal muscle mass obstructing the left ventricular outflow tract.

Cardiac catheterization delineates the site of the obstructive left ventricular lesion as at the septum rather than at the aortic valve. The obstruction by the muscle mass may not be evident until the patient is exercised or receives an intravenous infusion of isoprotenol. Digitalis, Valsalva maneuvers, and the compensatory beat after an extrasystole will also aggravate the obstruction.

The hypertrophic left ventricle has low compliance and a low cardiac output. Despite normal coronary arteries these factors determine the symptomatology and eventual prognosis.

Intraspinal Arteriovenous Anomalies — Love et al. Page 255

The treatment of arteriovenous anomalies of the spinal cord has been disappointing, but recently Love et al. have had the experience of occluding the anomalous arteries after demonstrating them with retrograde aortograms. In the past there has been little hope for patients with this type of anomaly, and for the most part they have progressed to become paraplegic.

Treatment of Multiple Sclerosis — Grand Rounds Page 323

The treatment of multiple sclerosis has on the whole been unsatisfactory, but well controlled studies suggest that ACTH can provide some benefit in the treatment of the acute exacerbations of the disease. There are very few side effects, but the possibility of developing adrenal insufficiency during ACTH therapy must be watched for.

Forensic Psychiatry — Wilson Page 345

The McNaughton rules, established in 1843, were a list of answers given by the judiciary to the House of Lords on questions of criminal responsibility: "To establish a defense on the grounds of insanity it must be clearly proved that at the time of committing the act, the party accused was labouring under such a defect of reason, from disease of the mind, as not to know the nature and quality of the act he was doing; or, if he did know it that he did not know he was doing what was wrong."

The Durham rule formulated by Judge Bazalon: "An accused is not criminally responsible if his unlawful act was the product of mental disease or mental defect." Under a different name, this rule was essentially established in 1887 in the state of New Hampshire by Judge Doe.

The difficulty with forensic psychiatry is that of adequately defining insanity.

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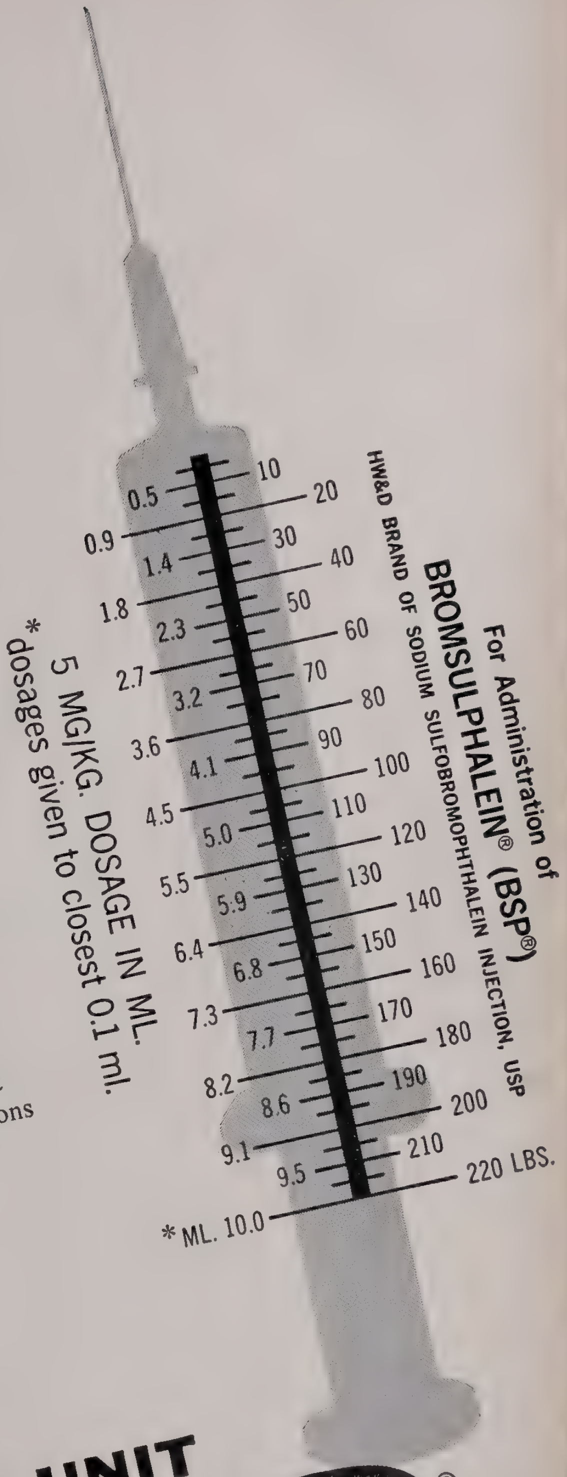

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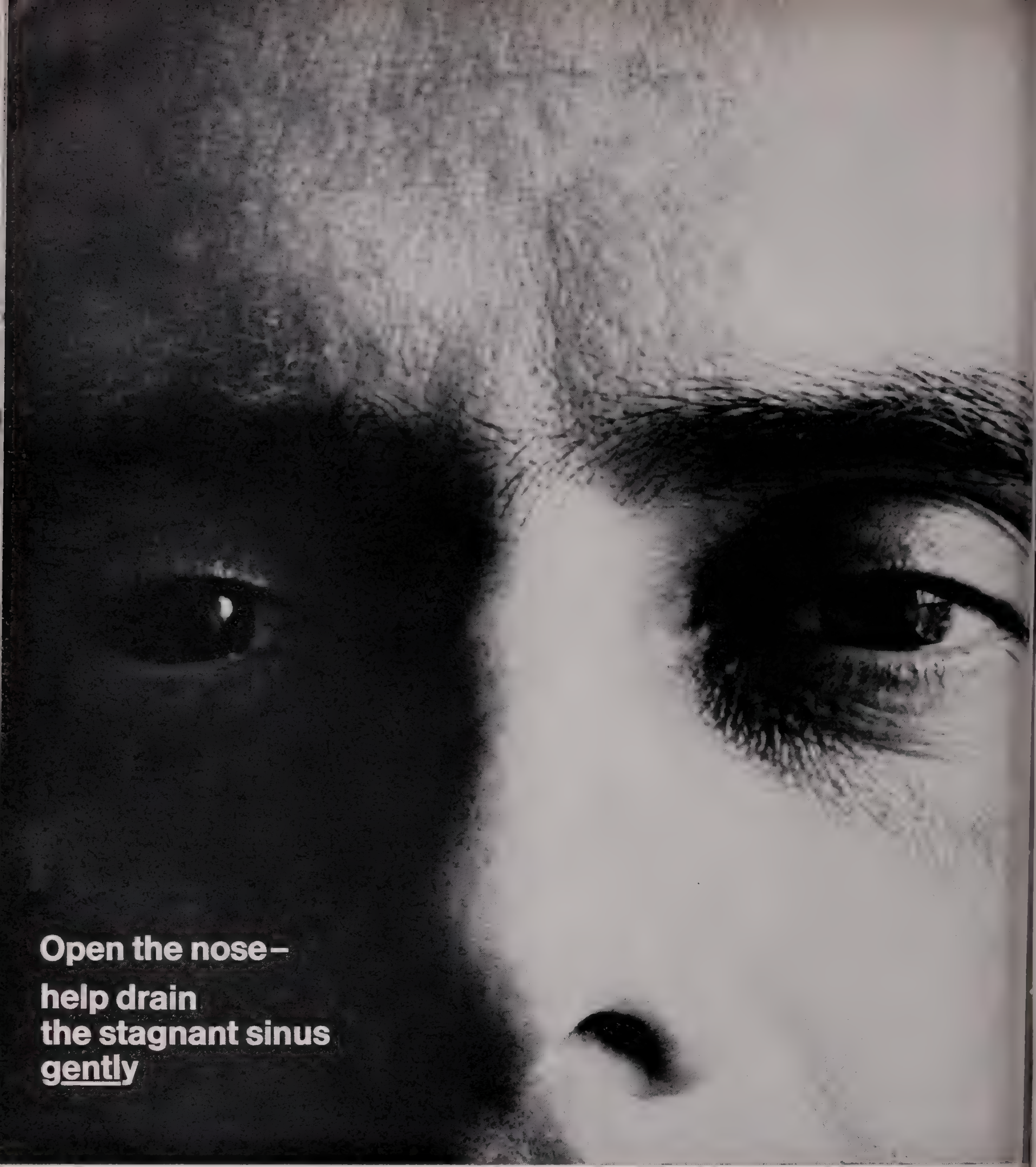

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*Proctor, D. F.: The Nose, Paranasal Sinuses, and Ears in Childhood, Springfield, Ill., Charles C Thomas, 1963, p. 34.

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President's Letter

In 1964 the House of Delegates of the Minnesota State Medical Association considered and approved a recommendation, developed after long discussion and hearings by the Committee on Medical Services, that component societies be advised of the rapidly developing need for utilization committee formation within each hospital staff. Further, the Committee was instructed from its experience to offer guidance and assistance to component societies and hospitals in their area, when requested. At that same time, several committees and councils of the American Medical Association were considering the same problem, and during the 1964 Clinical Convention adopted the recommendations of the American Medical Association Commission on the Cost of Medical Care. Included in these recommendations was the statement "the state and local medical societies should urge and assist the medical staffs of hospitals to form utilization committees." Basically, this was the same policy adopted by the Minnesota State Medical Association, and the same recommendation to hospital staffs.

Since the passage of Medicare legislation, the voluntary aspect of the development of utilization committees has changed and is now written into, and required by, Federal law.

As of this writing, many of the same objections, which our committee heard from individual physicians and spokesmen for organized physician groups, are still being heard. Now, however, these concerns and objections are not local in origin, but because of the compulsion in the law itself are originating in every area in which the law is to be applied.

Following the passage of the Medicare bill, prior American Medical Association intensive study and conclusions with reference to utilization committees crystalized in the inclusion of this topic in the agenda of Technical Advisory Committee #3 (Provider Participation). Three meetings of this committee with representatives of the Social Security Administration were held during November and December of 1965. At the first meeting a pattern of what was to follow developed. Strong objections by the American Medical Association group to implications in drafts prepared by the Social Security Administration Staff that state agencies might have the responsibility to review these utilization plans to determine effectiveness by review of select or sample cases, resulted in the statements that: (1) physicians cannot cooperate with such intervention by government agencies, (2) the role of fiscal intermediaries should be maximized and that of state agencies minimized, and (3) proposed duplication of fiscal intermediaries would work against compliance and cooperation. Further, the American Medical Association group requested that H.E.W. Secretary Gardner, the General Counsel, and the Health Insurance Benefits Advisory Council be advised that "the following strong recommendations are brought to your attention:

1. That utilization review must be recognized as a professional concern.

2. That intrusion into matters of professional committees by government agencies is without precedent and in conflict with the

Continued to page 451.

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The Incompetent Cervix*

WILLIAM B. STROMME, M.D.
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Minneapolis, Minnesota

SELDOM IN our lifetime of practice are we witness to outstanding medical achievements. Probably the best known in our field of obstetrics and gynecology is the development by Papanicolaou of the cytologic study of the vaginal smear and of its subsequent clinical application in endocrinology and in cancer detection of the female generative tract. Of no less importance, we believe, to human salvage is the recognition of correctible causes of pregnancy wastage. As a specific example, in the past 20 years we have witnessed first, the recognition of the incompetent cervix and, subsequently, the development of successful methods of closure. In predisposed patients, the timely application of appropriate surgical measures can reverse an expected abortion rate of approximately 80 per cent to a salvage rate of approximately 80 per cent.

The occurrence of cervical incompetence, whether congenital or post-traumatic in origin, is a major complication of mid-pregnancy which may extend into the third trimester. Of an over-all pregnancy loss of 1.63 per cent in the second trimester, Stromme and Haywa[1] found the incompetent cervix to account for 16 per cent — second in known causes only to premature separation of the placenta. According to Taylor[2] the condition occurs about once in 500 pregnancies. However, once having occurred, the probability of recurrence in subsequent pregnancies is increased several-fold. The significance is not in the rarity of the phenomenon but in its predictable repetitiveness. For the individual so afflicted, this condition can be corrected with rewarding results.

The mechanism of cervical incompetence was first enunciated by Danforth[3] in 1947; he was the first to describe a congenital weakness or traumatic weakness of the fibromuscular junction at the site of the internal cervical os. It was his belief, since substantiated by others, that this weakness might result in a functional incompetence which would permit abortion in the second trimester. Palmer and Lacomme[4] in 1948, and independently Lash and Lash[5] in 1950, pioneered attempts at surgical correction of this weakness through reduction and closure of the presumed cervical scar. While Lash[6] has recently reported good results in over 95 cases, many of his postoperative patients failed to conceive. Believing that the defect might not be an anterior cervical scar, Shirodkar[7] developed the purse-string closure, first using chromic catgut; by 1955 — just 10 years ago — he reported his first series of 26 patients with only four failures. With similar yet independent thought, McDonald[8] introduced silk purse-string sutures for closure of the "traumatized" cervix; 33 of his series of 70 patients gave birth to surviving infants following his closure operation. Several modifications of the closure technique and different closure materials have been employed since these pioneer reports. Yet, with few exceptions, the basic cerclage* closure at the level of the internal os has prevailed as the choice of most practitioners.

---

*Presented at the 112th Annual Meeting of the Minnesota State Medical Association, May 17, 1965, in Minneapolis.

Widespread recognition of the importance of surgical correction of the incompetent cervix soon followed; and successful results[9-12] as published in the above and subsequent reports ranged from 66 to 100 per cent, varying more with selection of cases than with technique and closure material.

Indication for Use

This report is based on our experience with 51 patients, utilizing a modified Shirodkar operation. Selection of patients was based on significant past history, direct observation of developing cervical incompetence, or a combination of both. In a few instances, patients with unfavorable past histories had preconceptional investigation with Hegar dilators.

Functional Incompetence of Cervix

In agreement with several others, we believe that a functional incompetence exists when a Hegar dilator larger than a #6 size can be easily passed through the internal cervical os in the unanesthetized patient. When this was demonstrated, an elective operation was performed during the subsequent pregnancy.

History of Abortion Loss

Where there was history of late abortion losses in at least the last two pregnancies, the operation was done as a prophylactic procedure. The typical history was that of a "silent" labor, often preceded by a watery vaginal discharge and a sensation of pressure within the vagina. Except for occasional spotting, prior bleeding was notably absent. If examination in these patients found no other pathology to account for the losses, a modified Shirodkar operation was performed one or two weeks prior to the time of previous losses. Where the past history was not so clearly indicative of cervical weakness, and in all other patients, the operation was done as a therapeutic procedure. During the critical period patients were examined at weekly intervals and occasionally twice weekly, to ascertain developing cervical dilatation. At each visit, palpation and direct speculum examination was carried out; furthermore, patients were warned to report promptly any unusual watery vaginal discharge, spotting and/or "pressure" in the pelvis.

Dilated Internal Os

When a change in the cervix was noted, with the internal os dilated to but not beyond three or four cm., the patient was admitted to the hospital and the closure operation usually performed that same day. It is our[13] belief that dilatation of the cervix is slow and painless, and that opportunity is usually afforded to await these changes before performing the operation. Adherence to this policy, we believe, will justify the need for surgery when indicated and will obviate the need when not indicated.

Shirodkar Operation

A modified Shirodkar operation was performed 71 times in 51 patients. With but one exception, all were carried out during pregnancy. In six patients, in our earlier experience, it was necessary to repeat the operation during the pregnancy. In nine it was necessary to repeat the operation in subsequent pregnancies as a result of intentional or unintentional loss of cervical competence with vaginal delivery. Two patients have had the operation repeated in three successive pregnancies. Despite marked scarring in some instances the operation was performed in all patients with comparative ease. Blood loss averaged less than 100 ml. Transfusion was unnecessary.

While we have improved and on occasion modified our technique as we gained experience, the operation has remained fundamentally the same since first performed by us in 1957.

The Technique

The patient is placed in lithotomy position and vagina and cervix exposed. If the membranes are bulging, the patient is placed in deep Trendelenburg position to better facilitate the gentle replacement of the bag of waters above the level of the internal os. The cervix is grasped with sponge forceps and traction applied. Anteriorly, the mucosa is divided transversely at the level of the bladder reflection and the bladder dissected upward (Fig. 1-a). Using a curved Pean clamp, lateral submucosal channels are developed on both sides at this same level of the internal os. The cervix is then elevated, traction applied, and a similar transverse mucosal incision made posteriorly at this same level. Lateral submucosal channels are developed from below in the same manner as from above. Additional lateral traction is then made as the submucosal tunnel is completed using either a curved clamp or an aneurysm needle (Fig. 1-b).

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*See Test Your Word Score Page 447.

Fascia Strip

If the latter is used, silk sutures are attached and carried through the channels on each side. The posterior free end of the sutures is attached to opposite ends of the fascia or tape, and this in turn is carried up through the submucosal tunnels (Fig. 1-c). If a curved clamp is employed, the free end of the fascia is grasped on each side and withdrawn through the tunnels, thereby developing the closure loop. Being satisfied that the fascial loop is placed well up at the level of the internal os, it is drawn taut and tied. Internal palpation confirms that a competent closure has been achieved (Fig. 1-d). The fascia is anchored to the cervix posteriorly with transfixing sutures of 000 black silk; the knot is similarly transfixed to the cervix anteriorly. Finally, the anterior and posterior mucosal defects are closed with continuous locked sutures of 000 chromic catgut. We have employed ox fascia in most cases (38) because of its advantage in permitting vaginal delivery without need for its division at the time of labor. In two instances, tight closure could not be achieved. In these and in other instances where ox fascia was

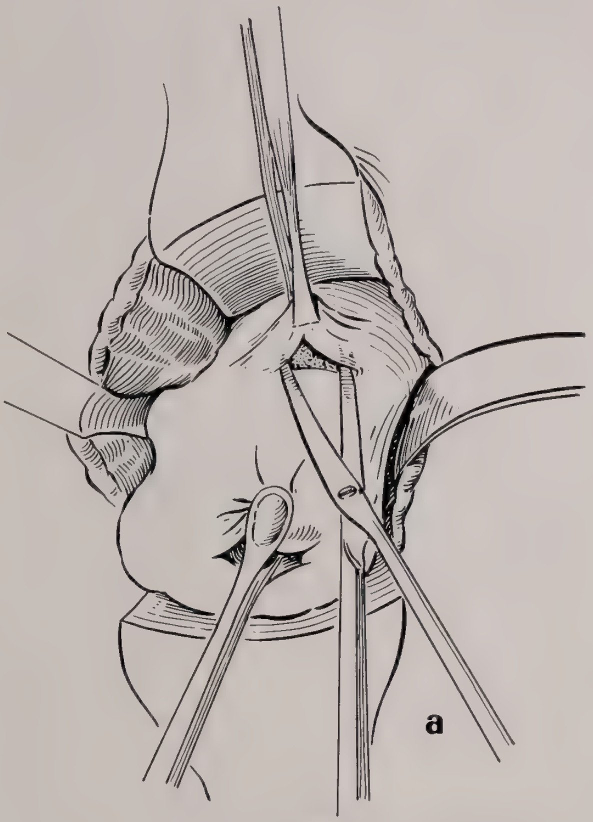

Fig. 1-a — Modified Shirodkar operation for cervical incompetence. Anterior vaginal mucosa incised at level of internal os.**

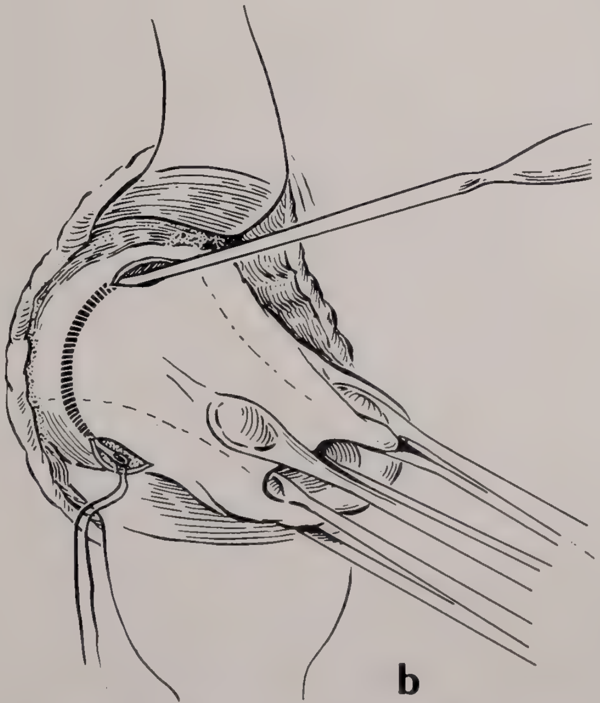

Fig. 1-b — Submucosal channel developed by curved aneurysm needle.**

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*Mersilene, Ethicon Co., Teflon, C. R. Bard Co.

**From Stromme, W. B., The Shirodkar Procedure for Cervical Incompetence. Lancet 82:304, 1962.

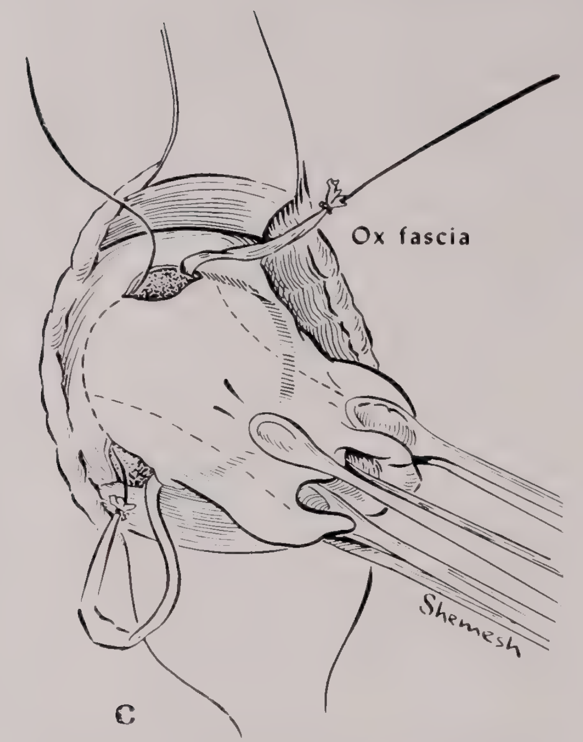

Fig. 1-c — Loop of closure material pulled up through submucosal channel.*

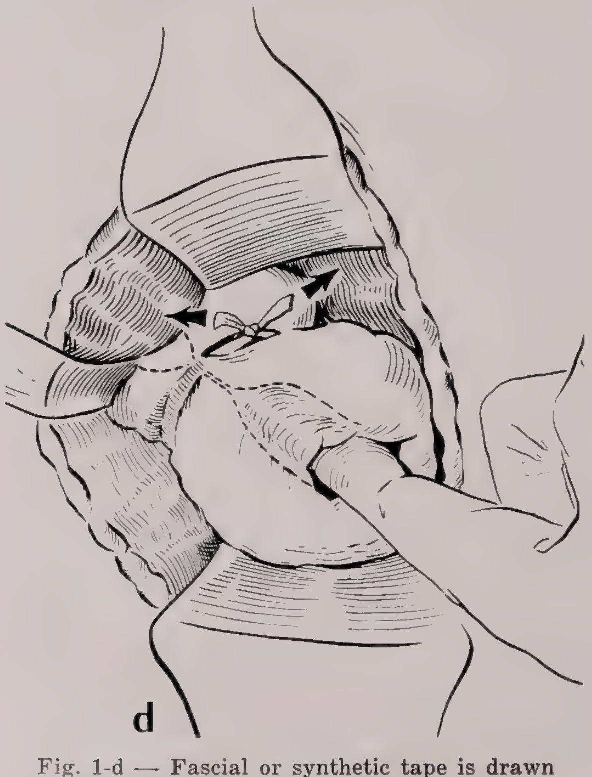

Fig. 1-d — Fascial or synthetic tape is drawn taut and tied, closing the internal os.*

not available, synthetic polyester fiber strips* or reconstituted collagen film was used.

Pre and Postoperative Care

Preoperative and postoperative care was essentially that for minor pelvic surgery. We no longer employ antibiotics except where specifically indicated; however, long-acting progesterone (Delalutin) 250 mg. is usually given postoperatively to control uterine irritability. The anesthetic of choice has been intravenous pentothal supplemented by nitrous oxide and oxygen by mask. Provided there are no uterine contractions, the patient is ambulated on the following day. Careful examination of the cervix to determine its competence is carried out before the patient is discharged from the hospital, usually on the sixth or seventh day.

The Delivery

Our preference is for vaginal delivery and the majority of patients, including all in whom ox fascia was utilized, were successfully managed in this way. Where nonabsorbable material was employed, delivery was accomplished either by division of the tape and vaginal birth or by cesarean section, depending on extenuating and individual circumstances as well as the condition of the cervix.

Subsequent Pregnancies

Management in subsequent pregnancies was individualized, with close observation and expectant Shirodkar operation performed only when indicated by developing incompetence. Except where nonabsorbable tape had been used, with division and/or removal, repeat operation was seldom required despite previous vaginal delivery. As an example, our first patient with closure employing ox fascia was delivered by cesarean section at 38 weeks. She subsequently delivered vaginally at 37½ weeks, although repeat section was scheduled. Two years later she again delivered vaginally and now is once again pregnant with expectation of term vaginal delivery.

Results

This report is based on 51 patients with incompetent cervix treated by modified

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*From Stromme, W. B., The Shirodkar Procedure for Cervical Incompetence. Lancet 82:304, 1962.

Shirodkar operation on 71 occasions (Table 1). The average patient age was 31 years. Nearly one third (29 per cent) of the patients were 35 years or older. Past obstetric history was characterized by repeated losses, largely in the second trimester. Less than 20 per cent had living children. Forty-seven (77 per cent) gave no history of previous trauma and it was presumed that incompetence was based on congenital defect (Table 2). Previous trauma was noted in 14 patients; the several factors are listed. Significantly, two followed amputation of the cervix, one for chronic infection and the other following high amputation for squamous-cell carcinoma in situ.

Basis for the cerclage operation was about equally divided between prophylactic (52%) and therapeutic (48%) indications (Table 3). All were carried out in the second trimester, as early as 12½ weeks (previously amputated cervix) and as late as 28 weeks (therapeutic, previous failure). Average duration of pregnancy was 19 weeks with the mode at 20 weeks. For several years ox fascia was not available; during this time polyester fiber strips and other synthetic materials were used. Because of its predictable surety, which was not always obtained with ox fascia, we have lately preferred synthetic tapes for closure of the previously traumatized cervix.

Complications

The operation was virtually free of complications. There were no instances of associated hemorrhage and accordingly no need for blood replacement. Average blood loss was less than 100 ml. There was only one instance of amnionitis and no systemic postoperative infections. The membranes ruptured during the course of the operation on only one occasion, and this, unfortunately, occurred near the conclusion of the operation as the purse-string fascia was being tightened.

Eighty-four women became pregnant following the initial Shirodkar operation (Table 4). Of these, four are currently pregnant; four others lost subsequent pregnancies as early abortions, including one ectopic pregnancy. A total of 61 (74%) surviving infants have been delivered.

TABLE 1
Summary of Patients with Incompetent Cervix

Number of patients		51
Age (22 to 42 years)	Average	31
Total Previous Pregnancies		253
Total Previous Losses		205*
Total Living Children (prior to operation)		48 (19%)

*93% were late abortion or pre-viable prematures.

TABLE 2
Etiology of Incompetent Cervix

Congenital		47
Previous Trauma		14
D & C's	8	
Forceps Delivery	2	
Amputated Cervix	2	
Cervical Myomectomy	1	
Cervical Laceration	1	

TABLE 3
Modified Shirodkar Operation for Incompetent Cervix

Operations Performed		71
Prophylactic	37 (52%)	
Therapeutic	34 (48%)	
Duration of Pregnancy (12-28 wk.) Average 19 weeks		
Material Employed*		
Ox fascia	38	
Polyester Fiber Strips (Mersilene)	31	
Polyester Fiber Strips (Teflon)	2	
Collagen Film	2	
Complications		
Hemorrhage	0 (Average blood loss 100 ml.)	
Amnionitis	1	
Rupture of Membranes	1	

*Two band combinations were used in 2 cases.

TABLE 4
Results Following Modified Shirodkar Operation

Total Pregnancies*		84
Total Surviving Infants		61 (74%)
Failures (gross)**		15 (18%)
Failures (corrected)***		10 (12%)
Etiology:		
Premature separation of the placenta	3	
Technique	3	
Premature rupture of membranes (Overactivity)	4	
Submucous Myoma	1	
Unexplained	3	

*Four are currently pregnant; four had subsequent early abortions, including one ectopic.

**Five have subsequently carried pregnancies to term following repeated operation; a sixth is currently six months pregnant.

***Premature rupture of membranes, operation closure secure; viable infants, death from (1) Hyaline Membrane Disease (2) Mongolism.

Failures

In terms of failure of survival, the gross failure rate was 18 per cent (15). Five of these women subsequently conceived and, after repeat Shirodkar operations, successfully carried to term; a sixth woman is now six months pregnant. When corrected on the basis of maintaining a satisfactory competence of the cervix following the operation, there were only 10 failures. Premature rupture of membranes occurred in four instances following over-activity; in these, it was necessary to divide the synthetic fiber band to permit vaginal delivery. Included was a viable infant of 1640 gm. who died of hyaline membrane disease; a fifth infant was delivered at term but died on the fifth day from mongolism. The attributable causes for these failures are the following: premature separation of the placenta (3), faulty technique (3), premature rupture of membranes (over-activity) (4), submucous myoma (1) — the operation was probably not indicated in this case despite two previous second trimester losses, — and unexplained (3).

Method of Delivery

Vaginal delivery of surviving infants (and all nonviable births), was successfully performed in 44 patients (72%) (Table 5). In 11 of these it was necessary to divide the nonabsorbable tape early in labor. In only one patient was there hemorrhage (1500 ml.) related to laceration and bleeding from the cervix following tearing and slippage of the polyester fiber ring. Seventeen patients were delivered by cesarean section (16 as elective operation, one following a period of trial labor).

TABLE 5
Delivery Surviving Babies Following Shirodkar Operation

Vaginal Delivery (Tape divided in 11)	44 (72%)
Cesarean Section	17 (28%)
	61

Post-Partum Findings

Post-partum studies were performed on 19 patients to determine whether or not cervical competence had been destroyed by vaginal delivery. All had been closed by ox fascia. The same Hegar dilator test was employed as earlier described. All tests were made from seven to 77 weeks post partum, with average at 12 weeks. In 14 patients the cervical competence was maintained; however, in five a #7 Hegar could be passed with ease, indicating loss of competence. Two of these subsequently became pregnant, and competence of the cervix was again restored with the use of polyester fiber tape.

Discussion

In the majority of cases previous cervical trauma does not play a role in the etiology of the incompetent cervix. We have reserved the operation for those women with developing cervical dilatation. Admittedly, we have on one or two occasions missed the opportune time for correcting the weakness, and in one instance, with the cervix four cm. dilated, membranes inadvertently ruptured during the course of the operation. On the other hand, in several cases with unfavorable histories, we have been surprised in our weekly examinations to follow these patients through to term without need for closure. Experience has taught us that cerclage at a higher level, is preferable; it is not necessary to transfix the cardinal and uterosacral ligaments, as suggested by Mann.[14] Except for the one patient with high amputation of the cervix where the vaginal approach failed, there would seem to be no justification for the abdominal approach, as recommended by Benson and Durfee.[15]

Where the cervix is of sufficient length and is unscarred, we prefer to use ox fascia as the closure material, as it handles well and can be drawn to a tight closure of the internal os. In time it is replaced by fibrous connective tissue which maintains a competence to term and yet allows vaginal delivery.

Where the cervix has been deeply scarred with previous lacerations, polyester fiber is preferable to tape, since under these circumstances, it may be possible to achieve a tighter, more lasting closure.

Our preference is for vaginal delivery. Thus, except for patients with marked cervical scarring or for those with additional obstetric indications, cesarean delivery would hardly seem warranted, except in the interests of maintaining a competent cervix for future pregnancies.

Conclusions

Incompetent cervix is a well-recognized cause of pregnancy wastage. It may be of congenital or traumatic origin.

Corrective surgery may be performed on a prophylactic or therapeutic basis; in the latter circumstances, frequent examinations will permit timely intervention.

The modified Shirodkar operation is easily performed with virtually no risk to patient or fetus; and a good cerclage technique is probably more important than the choice of closure material.

Vaginal delivery is practical in most cases. Division of the tape will be necessary only where nonabsorbable material is employed. Cesarean delivery may be preferred when the cervix is badly scarred and for other obstetric indications.

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13-15 May be secured from the author or the reprints.

Old Age

Thor, who loved to extoll his physical powers, had been outdone by King Utgard-Loki, who had wagered with Thor that he could not lift from the ground a mere cat which was found to be Midgard, the formidable world serpent.*

After this defeat Thor was anxious to redeem himself, and he offered to wrestle with any of the giants that might be assigned to him. The king replied that it was beneath the dignity of any of his men to compete with the likes of Thor; instead, he called in an aged female, Elli (Annodomini), to wrestle with his guest. Chagrined, but assuming it would require only a smidgen of strength to seize and floor her instantaneously, Thor laid on but couldn't budge the old lady. Instead, after calmly standing her ground for a while, she abruptly forced him down onto one knee — whereupon Utgard-Loki called off the match.

So, twice had the doughty God Thor been ignominously vanquished: once by a mere cat and once by an old woman!

However, things are not always what they seem.

As for Elli, she was Old Age — and what man had ever bested her!

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*See Minnesota Med 49:295, 1966.

Profunda Femoris-

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REVASCULARIZATION PROCEDURES in the lower limb for arteriosclerotic occlusion of the superficial femoral artery must be individualized because of variations in the extent of disease found to be present on surgical exploration. Whether the occlusion is corrected by endarterectomy or bypassed with a plastic prosthesis or autogenous vein depends to a degree on the personal preference of the operating surgeon.[1-3] Endarterectomy has proved to be successful, but if it is to be performed over any considerable length of vessel, bits of roughened intima may be left behind with a propensity towards reocclusion. The ready availability of the plastic prosthetics has given great impetus to the growth of peripheral vascular surgery, but long term follow-up studies[4,5] have revealed a rather high rate of late occlusion. The problems of excessive foreign-body reaction and infection are real and mitigate against the use of prosthetics below the inguinal ligament.

During recent years there has been a general trend towards the use of the vein autograft sewn between the common femoral and popliteal arteries.[6] This procedure, although time-consuming, avoids the necessity of using a foreign body and involves a minimum of intimal trauma. However, in order to preserve viability and usefulness of the limb, there are certain instances wherein a variation of this procedure has merit: if an infection has occurred in a previously performed femoral popliteal shunt, it may be desirable to avoid the infected field by constructing another shunt in a clean field prior to removal of the contaminated graft. A technique for constructing a profunda femoris-popliteal shunt through a posterior approach has been previously described.[7]

A second circumstance in which an alternative procedure may be desirable is in the patient who has had a prosthetic aortofemoral graft successfully inserted, and who subsequently develops a superficial artery occlusion requiring a lower limb revascularization procedure. Exposure of the lower end of the previously well incorporated graft should be avoided as this increases the risk of infection and anastomotic breakdown.

A suitable alternative procedure has proven successful wherein the saphenous vein was removed from the thigh and used as a profunda femoris-popliteal shunt around the occluded superficial femoral artery. Exposure was gained through the same incision required to remove the vein but without dissecting out the previously incorporated graft, the common femoral artery, or the occluded superficial femoral artery.

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Popliteal Shunt

Medical Approach

Case History

A 59-year-old male had a knitted Teflon iliofemoral bypass graft inserted on June 19, 1963, for an occluded left external iliac artery. He had complained of intermittent claudication in the left calf prior to surgery but was asymptomatic afterward.

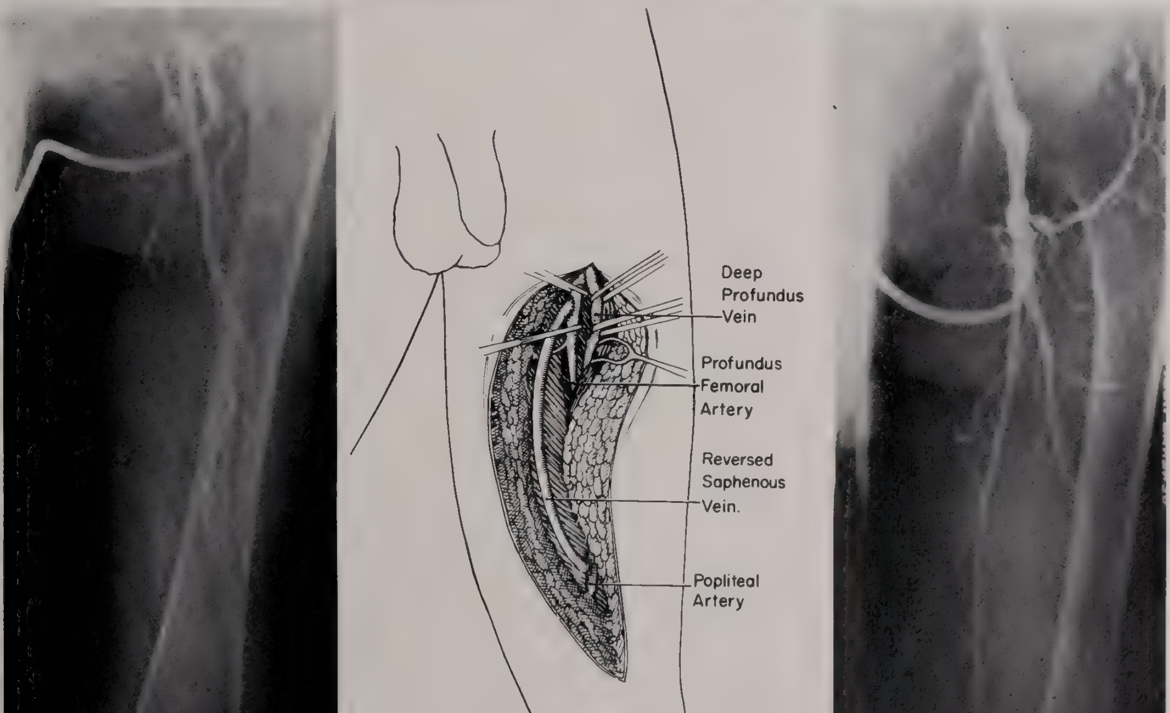
Deep
Profundus
Vein
Profundus
Femoral
Artery
Reversed
Saphenous
Vein.
Popliteal
Artery

Fig. 1 — (a-left) Preoperative arteriogram demonstrating occlusion of the superficial femoral artery (b-middle) Diagram depicting the operative procedure (c-right) Arteriogram three days following surgery.

His relief lasted for over a year, but he noted the gradual return of similar symptoms and was admitted on March 20, 1965, for evaluation. At this time the Teflon shunt was working well as determined by a strong femoral pulsation; however, there was no palpable pulsating vessel below this point. A femoral arteriogram (Figure 1-a) demonstrated an occluded superficial femoral artery, an open popliteal artery, and a large profunda femoris artery.

The Surgical Procedure

At surgery on March 23, 1965, an incision was made over the course of the saphenous vein in the left thigh and the vein subsequently removed and placed in a solution of saline with 1% procaine and heparin added. The procedure was then continued by retracting the sartorius muscle superiorly and laterally and dissecting downward on the anterior surface of the adductor longus muscle until the deep femoral vessels were reached just before they dipped posteriorly behind the adductor muscles (Figure 1-b). A very adequate exposure of the profunda femoris artery was obtained after dividing several small branches of the deep femoral vein. The popliteal artery was dissected free, carefully preserving its collateral branches, and the saphenous vein reversed and sewn end to side to the popliteal artery and end to side to the profunda femoris artery. A strong pulsation was achieved when the vascular clamps were released. After surgery the dorsalis pedal pulsation was present, and a repeat arteriogram (Figure 1-c) demonstrated a functioning shunt.

Four days after surgery the patient suffered a myocardial infarction and had several mild ischemic cerebral episodes which may indicate carotid artery disease. When last seen three months after surgery, the shunt was open and working well, as determined by a lack of claudication on walking, a palpable dorsalis pedal pulse, and a warm foot.

Discussion

The incision made is the same as that for a femoral popliteal shunt with the exception of the superior portion of the wound where the dissection is deep and medial to the superficial femoral and common femoral arteries. The profunda femoris artery is exposed approximately two to three inches below its origin, and the anastomosis at this point can be made without difficulty. The graft is placed in a gentle arc over the sartorius muscle or tunneled under the muscle if the angle appears too sharp.

There are two advantages to this approach. First, the profunda femoris artery is frequently soft and pliable, whereas the common femoral and superficial femoral arteries are commonly arteriosclerotic; in addition, occlusion of the superficial femoral artery is often accompanied by an enlargement of the profunda femoris artery, making it more suitable as a source for a shunt. Second, the previously well incorporated graft need not be exposed. A theoretical disadvantage is that the dissection which is required about the deep veins of the thigh could predispose to subsequent venous thrombosis.

Summary

There is reason to avoid exposure of a previously well incorporated aorto-femoral or ilio-femoral prosthetic shunt when a second and lower limb revascularization procedure is required. A medial approach to the profunda femoris artery was utilized in order that the previous graft could be avoided and the saphenous vein was removed through the same incision and used as a profunda femoris-popliteal shunt.

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Derivatively Speaking

Delirium — from Latin *de* (from) + *lira* (track) ; hence "off the track."

Cardioversion of Ventricular Tachycardia Following Myocardial Infarction[*]

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VENTRICULAR TACHYCARDIA is a rapid, fairly regular rhythm caused by stimuli originating from one or more irritable foci in one of the ventricles. The rate is commonly between 150 and 200. Ventricular tachycardia is believed to occur in two to four per cent of myocardial infarctions and is a serious complication.[1] It results in further impairment of myocardial blood flow and in decreased cardiac output with resultant fall in blood pressure. These factors potentiate each other in a vicious manner. Ventricular tachycardia may proceed without warning to ventricular fibrillation or asystole and can be either the cause of an infarction or a complication thereof. Early recognition and treatment is essential.

Etiology

Although paroxysmal ventricular tachycardia most commonly occurs in severely diseased hearts we now know with the help of the long term electrocardiographic monitor that this arrhythmia is more common in apparently healthy persons than earlier supposed. Semler has reported the case of a 16-year-old boy who had four attacks of ventricular tachycardia recorded on the electrocardiographic monitor during an examination at school.[2] However, extensive cardiac evaluation including several exercise tests failed to reveal any abnormality. The patient has been symptom-free since administration of quinidine.

The most common conditions associated with ventricular tachycardia are:

1. Coronary heart disease with or without myocardial infarction, and hypertensive heart disease.

2. Heart surgery and cardiac catheterization.

3. A miscellaneous group, including rheumatic fever, myocarditis, myocardosis[‡] and

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[*] Presented before Minnesota Society of Internal Medicine, May 8, 1965.

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[‡] See Test Your Word Score Page 447.

Wolff-Parkinson-White syndrome (extremely rare).

4. Electrolyte disturbances such as hyperpotassemia and also digitalis, pronestyl (procaine amide) and quinidine intoxications.

5. Unknown.[3,4]

The frequency of the different causes for ventricular tachycardia has been reported in a review of 107 cases by Armbrust and Levine.[5] They found this arrhythmia associated with coronary heart disease in 74%, with rheumatic heart disease in 8.4%, and with no known heart disease in 12%. The remaining group consists of miscellaneous types.

Treatment

Massage Carotid Sinus

Vagal stimulation with the use of carotid sinus massage should be attempted in all instances of supposed ventricular tachycardia. Conversion of the arrhythmia or transient slowing of the rate by this mechanism strongly suggests a supraventricular origin. Absence of effect by carotid sinus massage suggests but does not prove the presence of a ventricular arrhythmia.

Drugs

Pronestyl or quinidine is the drug of choice in this arrhythmia,[6,7] the former being preferable because of its greater safety during intravenous administration. The recommended dosage is 2000 mg. of pronestyl in 100 cc. 5% dextrose in water with an infusion rate of 100 mg. every two to five minutes. A second bottle containing 100 mg. aramine (metaraminol) in 500 cc. 5% dextrose in water should be connected and ready for use if a significant drop in blood pressure should occur. During the infusion of pronestyl continuous electrocardiographic monitoring should be obtained, or at least a short run every minute. If widening of the QRS complexes develops, suggesting toxicity to the pronestyl, the rate must be slowed or the infusion stopped.

Suggested oral maintenance dosages are 500 to 750 mg. of pronestyl every four hours, or 200 to 400 mg. of quinidine every four hours. These initial dosages can be gradually tapered.

Other drugs have been used in the treatment of ventricular tachycardia, such as xylocaine (diethylaminoacet-2,6-xylidide hydrochloride) and dilantin (diphenylhydantoine).[8,9] Dilantin in particular seems to be promising in this field as well as for certain supraventricular tachycardias. In personal communication Dr. Richard Langendorf has described one case of ventricular tachycardia that initially did not respond to pronestyl but after an unsuccessful electric countershock was easily converted with pronestyl.

Disadvantages of Drug Therapy

Some of the disadvantages of drug therapy are that:

1. Ventricular tachycardia may not respond favorably to these drugs in any dosage and valuable time may be lost in arriving at this conclusion.

2. The addition of intravenous fluid can impose an undesirable burden on a heart in borderline failure. This is especially true when large dosages of medication are required.

3. Severe toxic reactions to the medications may occur. Along with the desired effect of suppressing ectopic pacemakers, depression of normal cardiac contractility can occur, resulting in fall in blood pressure. This hypotension enhances the development of ventricular fibrillation. Asystole is seen more rarely.

4. It may be difficult if not impossible on the electrocardiogram to establish the origin of the ectopic pacemaker. If supraventricular tachycardia with widened QRS complexes is erroneously diagnosed as ventricular tachycardia, pronestyl will likely do nothing. If ventricular tachycardia is erroneously diagnosed as supraventricular tachycardia with widened QRS complexes, the administration of intravenous digitalis is hazardous.

There have been many successful reports on the use of the alternating current defibrillator in terminating ventricular tachycardia, primarily by Zoll and his associates.[10-13] The use of synchronized capacitor discharge as a method to terminate this arrhythmia was first described in 1962 by Lown.[14] Our case reports are with the use of the Lown Direct Current Cardioverter.

Cardioversion

The application of brief high voltage direct current across the intact chest so timed as to avoid ventricular fibrillation depolarizes the heart muscle and ectopic foci, allowing the normal sinus pacemaker to take over. This assumes: a) The factors initiating the arrhythmia are different from the factors sustaining it, and b) The normal sinus pacemaker is intact and able to take over: i.e., you do not have the "sick sinus syndrome."

Advantages

Cardioversion by this method is simple, precise and immediate; it does not depress cardiac rhythmicity or contractility; it is effective in all types of arrhythmias;[15-17] and there are no documented reports of myocardial damage either experimentally in dogs or in human beings. This includes cases of myocardial infarction. The danger of embolization is probably similar to that after conversion of arrhythmias with drugs.

Disadvantages of the Cardioverter

Cardioversion is not invariably effective. A light general anesthetic is usually needed; but when as little as 50 Watt-seconds is used, it is not always necessary. It would seem prudent not to attempt the procedure except in the presence of an anesthesiologist or nurse anesthetist. The cardioverter stops but does not prevent recurrence of the arrhythmia, and precise familiarity with the equipment is essential. Lack of respect for high voltage electricity may lead to cardioversion of yourself or your associates without the benefit of programing the shock to peak of your QRS complex.

The exceptional safety of the Lown D.C. Cardioverter is due to the synchronization of the counter shock with the least vulnerable phase of the cardiac cycle, namely at the height of the QRS complex. Shocks administered on the upsweep of the T-wave are prone to produce ventricular fibrillation, and those at the termination of the QRS complex may result in atrial fibrillation.

Indications

The indications for drug therapy versus cardioversion are still somewhat controversial.[18,19] Initially, Lown used only D.C. Cardioversion in cases refractory to drugs. At present there seems to be an agreement to use cardioversion in those patients who do not respond to drugs within a short time and in cases in which the course is complicated by shock or pulmonary edema.

Diagnostic Features of Ventricular Paroxysmal Tachycardia[20]

The diagnosis of ventricular paroxysmal tachycardia is *suggested* when there is a rapid succession of three or more ventricular beats of bizarre contour, premature in onset and followed by a pause, with QRS complexes prolonged to more than 0.12 seconds and the ST-T opposite in direction to and often continuing directly from and into the QRS. The ventricular rhythm may be regular or irregular, and sometimes upright P-waves can be identified (in Leads II, III and AVF) at an independent and slower rate, or retrograde P-waves definitely follow the rapid ventricular complexes.

The diagnosis is *established* when there are occasional conducted beats with QRS less prolonged than in the beats of the tachycardia (ventricular *captures* by supraventricular impulses), or when there are ventricular fusion beats between ectopic and sinus impulses (except in the pre-excitation syndrome, WPW).

Normally, the cardiac impulse originates in the sinus node and spreads radially through the atrial muscle. In this spread, the A-V node is activated and transmits the impulses to the ventricles along the common bundle, its branches, and the Purkinje network.

While ventricular tachycardia can be suspected on the basis of a wide, bizarre contour to the QRS complexes, this is not absolute proof, since a nodal tachycardia can be associated with aberrant ventricular conduction or a pre-existent bundle branch block and thus cause prolongation of the QRS.

The two above mentioned electrocardiogram criteria for ventricular tachycardia are unfortunately rare. We were unable to demonstrate either of these beats: ventricular capture or ventricular fusion, in our cases.

Case Reports

Case #1

A 65-year-old farmer who developed anterior chest pain on May 1, 1964, was admitted to another hospital. His electrocardiogram was consistent with anterior myocardial infarction. The transaminase (S-GOT) was 150 units on the third hospital day. On the 18th hospital day he developed a heart rate of 162 with electrocardiographic evidence of probable ventricular tachycardia. This persisted for 17 days despite large dosages of pronestyl orally and intravenously. He was then transferred to the Bethesda Hospital. His blood pressure was 95 systolic, his heart rate was 150, and there was evidence of left ventricular failure. There was no response to carotid sinus massage. The electrocardiogram was believed consistent with ventricular tachycardia. Under pentothal anesthesia he received one shock of 100 Watt-seconds with conversion to atrial tachycardia with a 2:1 block. He quickly reverted spontaneously to sinus rhythm. Figure 1 shows the ventricular tachycardia and the re-established sinus rhythm. After the counter shock his blood pressure rose immediately to 120/75 and his general condition improved progressively. Two weeks after cardioversion he again developed atrial tachycardia with a 2:1 block with a ventricular rate of 132. He was given oral digitalis with reversion to sinus rhythm. He has remained well.

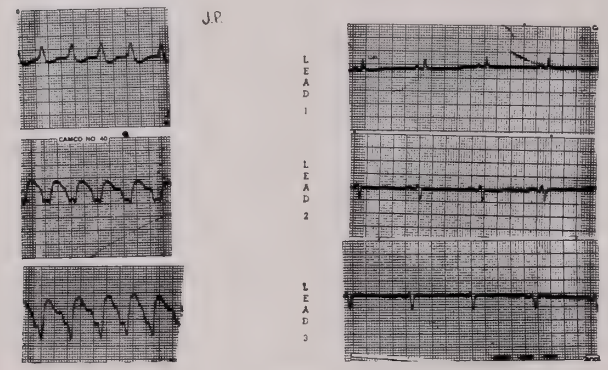

Figure 1

Case #2

A 65-year-old farmer was admitted to the Bethesda Hospital on July 2, 1964, with a history of severe chest pain several weeks earlier. He entered because of weakness of one week's duration. Blood pressure was 90 systolic. Chest X ray showed cardiomegaly and pulmonary congestion. His electrocardiogram showed a heart rate of 140 with widened QRS complexes which varied in configuration. No P-waves could be seen with certainty. Carotid sinus massage had no effect. Both pronestyl and quinidine were utilized without effect on the tachycardia, as seen in Figure 2. On the 12th hospital day a shock of 100 Watt-seconds was administered with establishment of sinus rhythm and immediate clinical improvement. The electrocardiogram was believed consistent with subacute posterior myocardial infarction. He was discharged in good condition 10 days after the cardioversion on oral pronestyl. He died suddenly two months later on the dance floor.

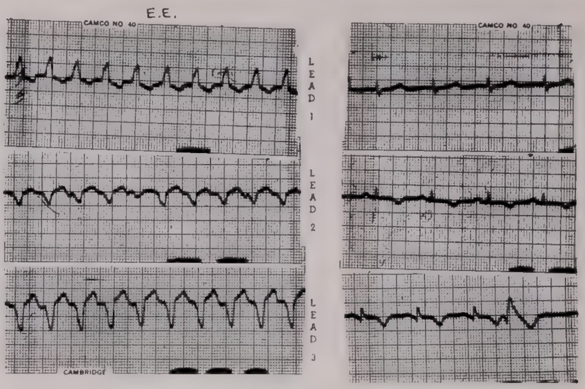

Figure 2

A 52-year-old printer, admitted to the Bethesda Hospital on September 9, 1964, had a history of pain in the chest and left shoulder five days prior to admission while mowing his lawn. Two days later he noted rapid beating of his heart. On admission his heart rate was 182 with an electrocardiogram consistent with ventricular tachycardia (Fig. 3). His blood pressure was 95 systolic. There were fine moist rales at the lung bases and tenderness over the liver. There was no response to carotid sinus massage. Pronestyl was administered intravenously without effect. Under pentothal anesthesia cardioversion was performed using a single shock of 100 Watt-seconds with conversion to sinus rhythm. His blood pressure rose quickly to 120/70 and he showed immediate clinical improvement. Subsequent cardiograms in the hospital were consistent with posterolateral infarction. He has remained well.

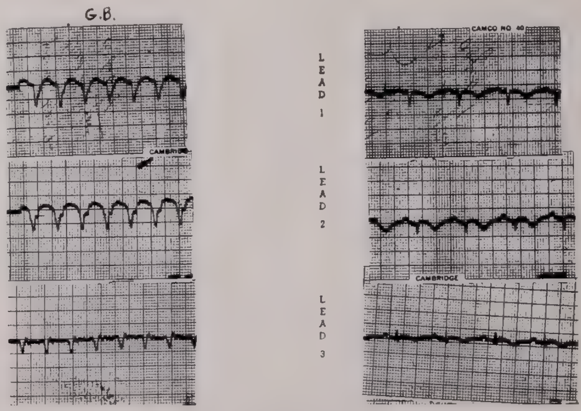

Figure 3

Case #4

An 80-year-old widow was admitted on April 12, 1965, with a history of vague chest distress. She was apprehensive and covered with cool perspiration. Her blood pressure was 100/70. Her heart rate was 204 and the electrocardiogram was interpreted as showing probable ventricular tachycardia. Repeated carotid sinus massage was ineffectual. Without a trial of pronestyl and without anesthetic, cardioversion was administered using 50-Watt-seconds. Sinus rhythm was then obtained. Her electrocardiogram before and after the counter shock are seen in Figure 4. Despite oral pronestyl, 250 mg. every four hours, she developed a recurrent tachycardia at a rate of 180 and was then noted to have a left hemiplegia. This arrythmia reverted to a slow sinus rhythm after pronestyl given intravenously. Six days later she developed atrial fibrillation with a ventricular rate of 190 and was given intravenous cedilanid with reversion to sinus rhythm. On the 11th hospital day she expired. Post-mortem examination showed evidence of recent as well as old myocardial infarctions. The transaminase (S-GOT) was 150 on the third hospital day.

Summary

Four patients with recent myocardial infarctions developed paroxysmal tachycardias believed to be of ventricular origin and were successfully treated with the Lown D.C.-Cardioverter. Three of the four had been refractory to other medical treatment. In seriously ill patients or in cases in which the electrocardiographic interpretation of a tachycardia is uncertain, the cardioverter fulfills a unique and useful role.

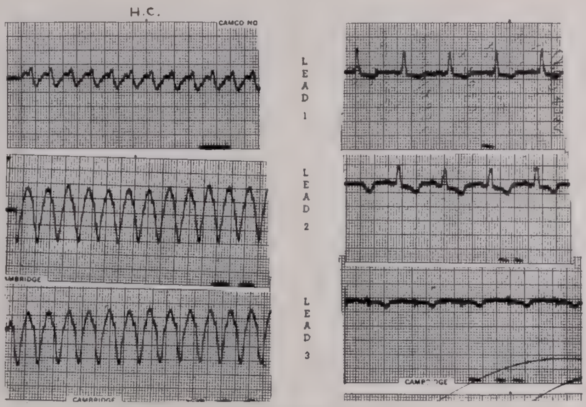

Figure 4

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9-20 May be secured from the author or the reprints.

On Extracting Bones

It will often happen in eating that fish-bones or other objects may be swallowed and get caught in some part of the throat. If they can be seen they should be removed with the forceps designed for that purpose. Where they are deeper, some recommend that the patient should swallow large mouthfuls of bread or other such food. Others recommend that a clean soft sponge of small circumference to which a string is attached be swallowed, and then drawn out by means of the string. This should be repeated until the bone or other object gets caught in the sponge and is drawn out. If the patient is seen immediately after eating, and the swallowed object is not visible, vomiting should be brought on by means of a finger in the throat or irritation with a feather, and then not infrequently the swallowed object will be brought up with the vomit. — Paul of Aegina (7th century)

You can't leave footprints on the sands of time by sitting down. — Dr. Karl Berns

The Doctor and Literature – Part III*

Oscar Wilde

Oscar Wilde, now acclaimed by discerning critics of all nations as the author of the finest farce in the English language, *The Importance of Being Earnest,* and of the poignant *Ballad of Reading Gaol,* was accused by the Marquis of Queensberry of having an unnatural relationship with Lord Alfred Douglas.

In a farcical trial before the prejudiced Justice Wills, Wilde was found guilty of homosexuality and sentenced to two years at hard labor, first at Wordsworth Prison and later at Reading Gaol.

Upon his release, Wilde was ostracised by the English philistines and after a few miserable years died in exile in Paris of cerebral meningitis, his creative genius destroyed in shamelessly borrowing money from his friends and cadging drinks from American tourists. Wilde's genius was purified and matured by his terrible suffering in prison which he summarizes in the lines:

> "We did not dare to breathe a prayer
> Or give our anguish scope
> Something was dead in each of us
> And what was dead was hope."

Henry Fielding

Henry Fielding, in his novel *Amelia,* gives a grimly realistic picture of medicine as practiced in the Eighteenth Century.

After the Apothecary Mr. Arsenic had failed to cure Amelia's child, another doctor was called in for consultation.

"The first thing the new doctor did was to cause all powders and potions to disappear at his command. For he said there was a much easier and nearer way to convey such stuff to the vault than by sending it first through the human body. He then ordered the child to be blooded, give it a clyster (an Eighteenth Century term for an enema) and some cooling physic and within three days cured the little patient of her distemper."

Sinclair Lewis

The ultimate evaluation of a novel is how it stands the test of time. In the forty years since it was published in 1925, *Arrowsmith,* by Sinclair Lewis still remains by critical acclaim the finest American novel about a doctor.

The tragedy of Sinclair Lewis' life was too much too soon. Born in Sauk Center, Minnesota, in 1885, the son of a country doctor, Lewis went to Yale in 1908. He was unpopular with his classmates, because he was a critical nonconformist. He travelled widely and became a free-lance writer who sold several popular short stories to the *Saturday Evening Post.* In 1914 he married Grace Livingstone Hegger, by whom he had a son, Wells, who was killed in the war in 1944.

Main Street, published in 1920, made Sinclair Lewis the most widely read and successful novelist of the Nineteen Twenties.

The novel was a scathing satire on Carol Kennicott's abortive efforts to jar the smug, self righteous town folk of Gopher Prairie, Minnesota, out of their provincialism and intolerance. After many heart-breaking failures Carol accepts her fate, but is determined her children will have a better life by escaping from Gopher Prairie.

Continued to page 542.

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*Continued from Minnesota Med 49:254, 1966.

Acute Cholecystitis

- Due to
- Coagulase
- Positive
- Staphylococci

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ACUTE CHOLECYSTITIS, most commonly initiated by impaction of a stone in the ampulla of the gallbladder,[1] is often accompanied by infection. Primary infection of the gallbladder is considered the etiology in the five to ten per cent[1] of patients with cholecystitis who have acalculous gallbladders. An occurrence of acute calculous cholecystitis due to coagulase positive *Staphylococcus aureus* is the basis for this report. We have been unable to find any previous report of such a case.

Case Report

A 26-year-old female was admitted to the University of Minnesota Hospitals in April, 1965, after four days of fever and severe right upper quadrant pain radiating to the right scapula. During the preceeding five years she had had several similar episodes, some with jaundice. She had never been hospitalized, had no known contact with hospital personnel, had never been treated with antibiotics.

Physical examination revealed a well-developed, well-nourished woman acutely ill with nausea, abdominal pain, and a temperature of 100°F. (rectal). An exquisitely tender mass was palpated in the right upper quadrant of the abdomen. Muscle guarding but no rebound tenderness was present. The hemoglobin was 15.8 gm. per 100 ml. and the white blood count 17,700 with 85 per cent neutrophils. The total serum bilirubin was 0.9 mgm. per 100 ml.

The patient was treated with nasogastric suction, intravenous fluids and tetracycline. Six hours after admission her temperature was 102.8°F. (rectal) and her white blood count 15,500. Twelve hours after admission her temperature was 103.6°F. (rectal), and her white blood count had risen to 22,600.

The patient was taken to the operating room where empyema of the gallbladder was found and a cholecystectomy performed. The gallbladder was distended with approximately 150 cc. of purulent material and contained 25 stones ranging up to 1.8 cm. in diameter. The operative cholangiogram was normal.

Culture of the gallbladder contents grew out coagulase positive *Staphylococcus aureus* in pure culture. The organism was sensitive only to methicillin and vancomycin in a concentration of 1.5 gamma per cc. The patient's temperature returned to normal on the second postoperative day, and she was discharged on the sixth day following surgery.

Comment

In addition to the role of chemical factors (pancreatic secretions, concentrated bile) the importance of bacterial infection in the etiology of cholecystitis has been studied. Spread of infection to the gallbladder by hematogenous[2,3] and lymphatic[4] routes has been postulated. Direct infection from the intestine via the common bile duct has also been proposed, but this does not seem practical in the majority of cases in which an impacted stone blocks the cystic duct.

---

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Dineen[5] has recently compared the theories of pathogenesis of gallbladder infection and concludes that the portal system is the most common route for delivering bacteria to the biliary tract. Small numbers of enteric organisms frequently enter the portal circulation from the intestinal tract, are removed from the blood by the reticuloendothelial system of the liver, and are excreted into the bile where they usually pass back into the intestine. In the presence of stagnant bile these organisms can multiply, stimulate leukocytic infiltration, and result in suppuration of the gallbladder.

The etiology of this patient's episode of cholecystitis can only be speculative. There was no evidence of a nidus of infection other than in the gallbladder, nor was there any history to suggest where she might have been exposed to a virulent strain of staphylococci. The possibility of such an atypical infection should be kept in mind when treating cholecystitis.

Summary

Cholecystitis in which coagulase positive *Staphylococcus aureus* can be cultured from the gallbladder is certainly unusual. Such an occurrence has not been reported previously.

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Brain Scanning with Neohydrin 197-Hg[*]

LUTHER O. WIGDAHL, M.D.[**]
J. MICHAEL GILSON, M.D.[†]
EDWARD V. STAAB, M.D.[**]
MERLE K. LOKEN, Ph.D., M.D.[‡]
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We have concluded, as a result of our observations and in agreement with other investigators,[1,2,3,4,5] that brain scanning is a valuable diagnostic procedure for detecting and localizing brain tumors and certain other non-neoplastic lesions.

During the 15-month period prior to January 1, 1965, 432 brain scans were performed at the University of Minnesota and Veterans Administration Hospitals utilizing the radioactive isotope 197-Hg tagged to Neohydrin. In 388 of these 432 scans we reached a positive or negative conclusion. However, for reasons that will be elaborated in the discussion, the remaining 44 cases had to be considered indeterminate.

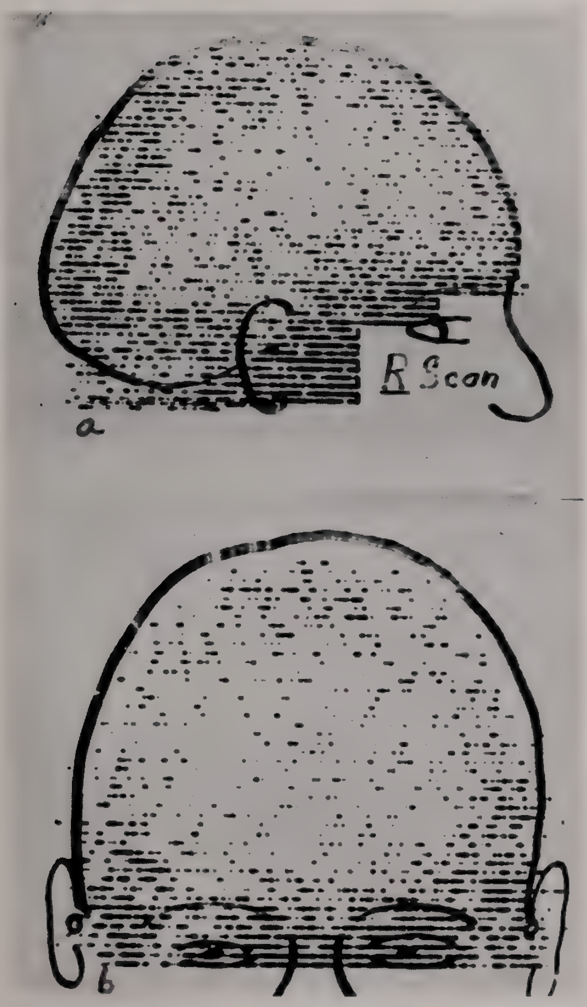

Fig. 1 — The normal brain scan. (a) Right lateral projection. (b) Frontal projection.

Procedure

Because of its simplicity, brain scanning is a procedure that can be performed with essentially no morbidity. 197-Hg Neohydrin is given intravenously in a dose of 10 microcuries per kilogram. Using the Picker magnascanner, we began scanning three to four hours after administration of the isotope and found that we were able to obtain two projections of the brain in about 1-1/2 hours. In certain cases additional projections or delayed scans at 24 hours were helpful.

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[*] From the University of Minnesota and Veterans Administration Hospitals, Minneapolis.

Supported in part by funds from the American Cancer Society (Institutional Grant) and the Graduate School, University of Minnesota.

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The Normal Brain Scan

In a normal patient without circulatory embarrassment or significant renal impairment, about 90% of the isotope is cleared from the circulation in about five hours; therefore, as shown in the normal brain scan of Figure 1, only a small amount of circulating isotope is present in the major venous sinuses such as the sagittal and sigmoid. In addition, some normal accumulation of the isotope is seen in the temporal and occipital musculature as well as in the nasopharyngeal mucosal area.

The Abnormal Brain Scan

In a brain scan showing an abnormal state of the brain the isotope localizes in other than normal areas because there has been an alteration of the normal "blood-brain" barrier by pathological conditions. The large accumulation of black dots in the frontal area of the brain clearly demonstrates such an abnormality in Figure 2. Incidentally, this represents a large metastatic brain tumor, and the size of the lesion on the brain scan correlates well with the actual size of the tumor in well-demonstrated lesions such as this.

The first category of abnormality consists of neoplastic lesions, both primary and metastatic. Non-neoplastic lesions[6,7] comprise the second category and include intracerebral hematomas, acute and chronic subdural hematomas, and cerebral vascular accidents that result in appreciable ischemia or infarction. To the experienced observer, most of

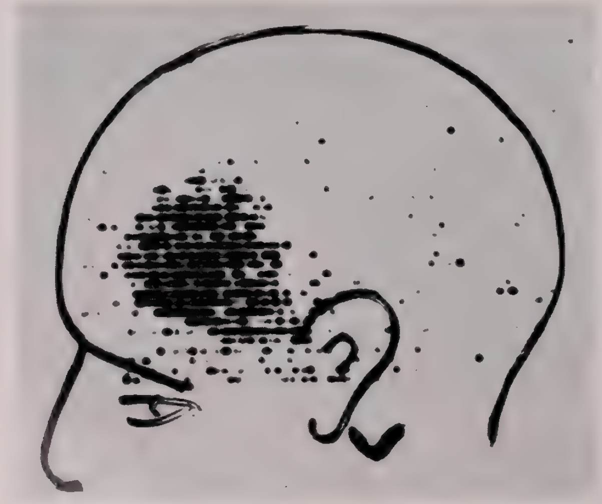

Fig. 2 — Positive brain scan, left frontal temporal area; metastatic tumor from undifferentiated carcinoma of the prostate.

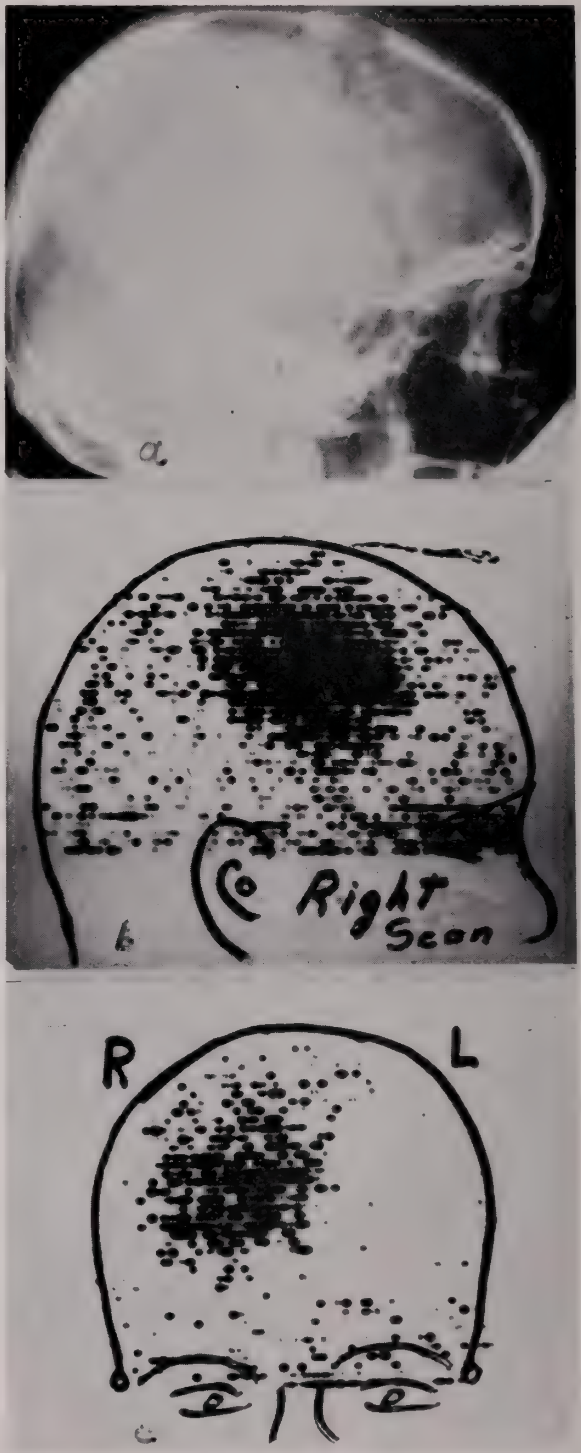

Fig. 3 — (a) Lateral skull demonstrating abnormal meningioma bone in parasagittal area. (b) Right lateral brain scan demonstrates large soft tissue component of meningioma, right frontal area. (c) Frontal projection.

these entities reveal a characteristic pattern; however, correlation with the clinical history and findings may be necessary for definitive interpretation.

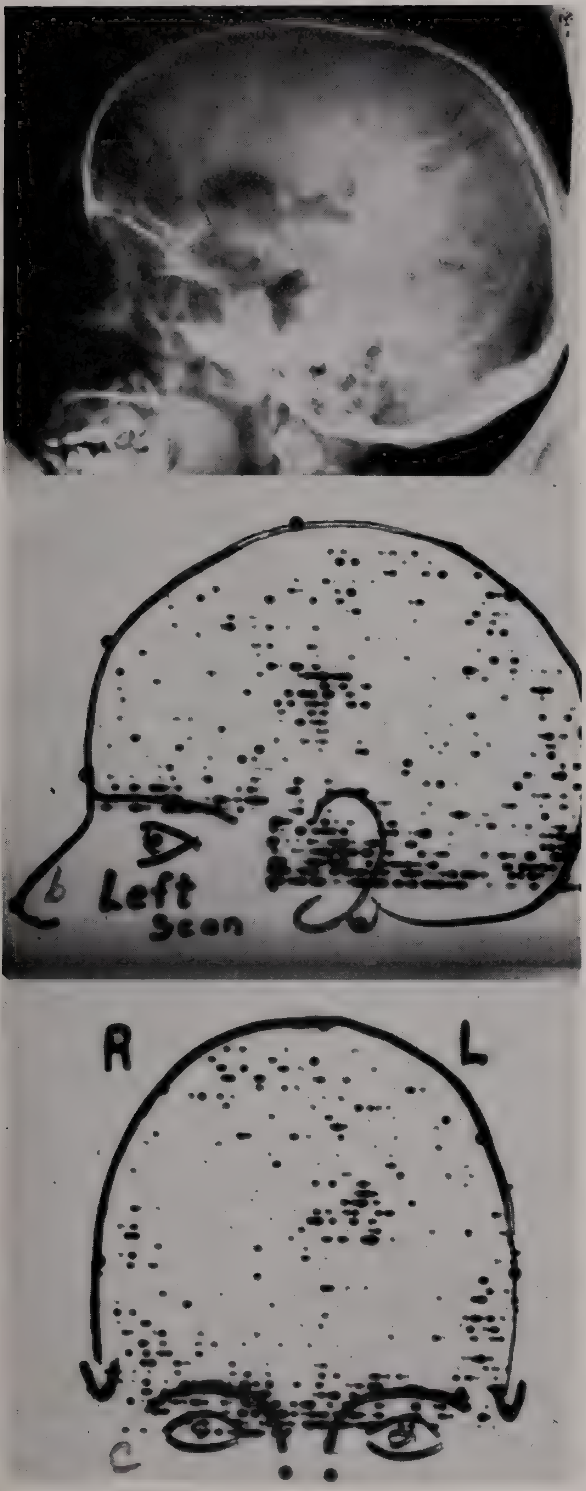

Fig. 4—Astrocytoma, Grade II. (a) Pneumoencephalogram reveals mass indenting roof of lateral ventricle. (b) Positive left lateral brain scan. (c) Frontal projection.

Brain Tumors

The lateral skull projection in Figure 3 reveals an abnormal area of bone in the frontal parasagittal area. The brain scan demonstrates well the large soft tissue component of the meningioma in the right frontal parasagittal area.

The lateral projection of the pneumoencephalogram in Figure 4 shows a mass indenting the roof of the lateral ventricle. The brain scan was also positive, giving good correlation with the localization seen on the pneumoencephalogram. This tumor proved to be a Grade II astrocytoma.

A few cases of brain tumor were demonstrated by brain scanning, although appropriate angiograms failed to reveal the lesion. The positive focus of black dots seen in the frontal parasagittal area in Figure 5 is an example. This proved to be a 3-cm. recurrent meningioma. The positive focus seen in the right cerebellar hemisphere in Figure 6 was also not localized by angiography and later proved to be a right cerebellar glioblastoma.

Metastatic tumors are also demonstrated in a high percentage of cases by brain scanning. A left carotid angiogram as shown in

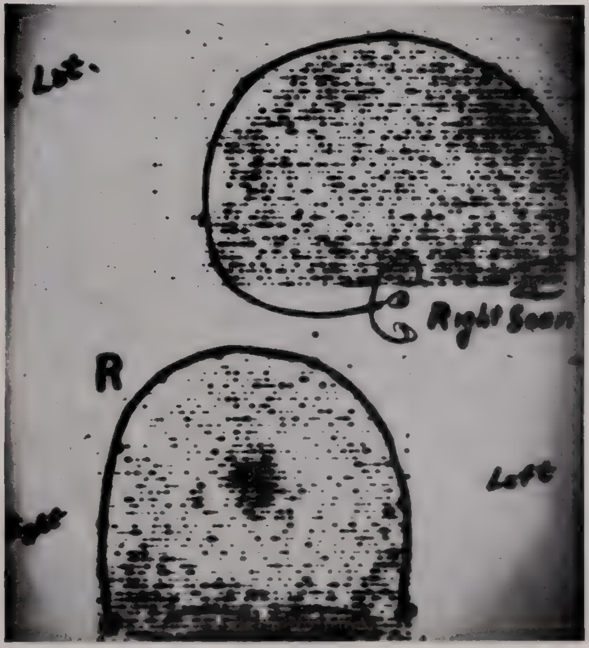

Fig. 5 — Recurrent meningioma, frontal parasagittal area, revealing a positive brain scan.

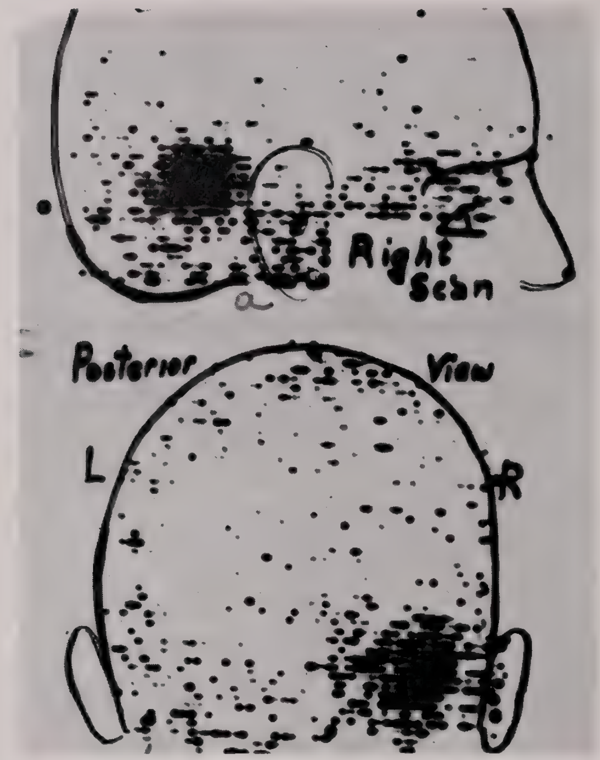

Fig. 6 — Glioblastoma, right cerebellum. (a) Positive right lateral scan. (b) Posterior view.

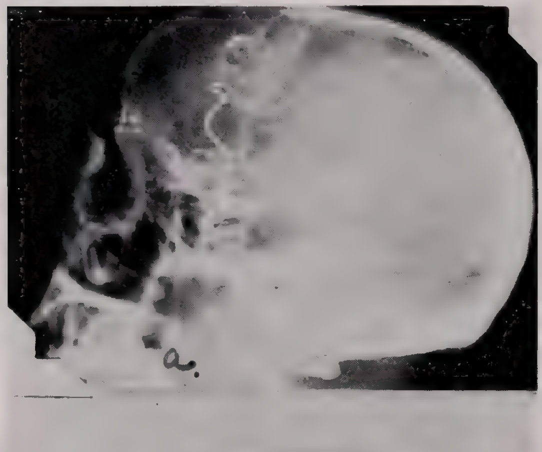

Fig. 7 — Metastatic tumor, left frontal lobe. (a) Demonstrated by left carotid angiogram. (b) Demonstrated by left lateral brain scan.

Figure 7 demonstrates a metastatic tumor in the left frontal lobe with abnormal vessels characteristic of tumor. The brain scan also localizes this lesion. In fact, when metastatic lesions were suspected, the brain scan was often the only special procedure performed. The 5-cm. metastatic lesion in the left cerebellar hemisphere, demonstrated in Figure 8, illustrates such a case.

Non-neoplastic Lesions

Positive brain scans were obtained of several patients having intracerebral and chronic subdural hematomas. As an illustration of this, the venous phase of a left carotid angiogram shown in Figure 9 reveals a left frontal subdural hematoma. The corresponding brain scan also reveals accumulation of isotope along the left lateral portion of the skull characteristic of chronic subdural hematoma. Another frequent abnormality giving a positive brain scan is cerebral throm-

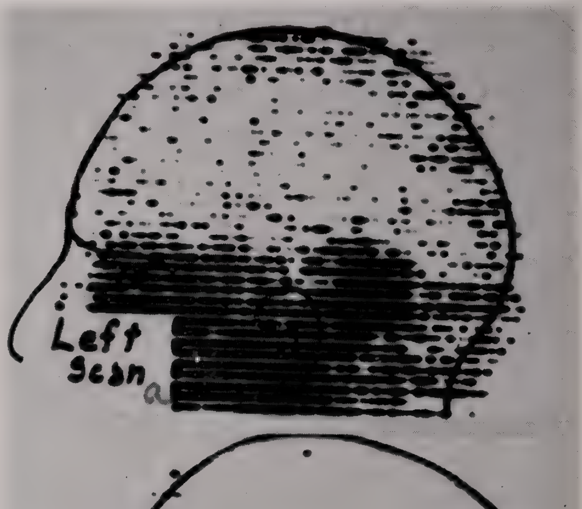

Fig. 8 — Metastatic tumor, left cerebellum. (a) Left lateral brain scan. (b) Right lateral brain scan.

bosis and infarction, as shown in Figure 10-a. The frontal projection of this scan, which is not included, reveals the typical diffuse pattern characteristic of middle cerebral artery thrombosis. A subsequent right lateral brain scan, Figure 10-b performed two months later, reveals complete clearing of this abnormal accumulation of isotope. This clearing after an interval of two to three months following the initial positive scan is typical of cerebral artery thrombosis. Such clearing would not occur with a neoplastic lesion.

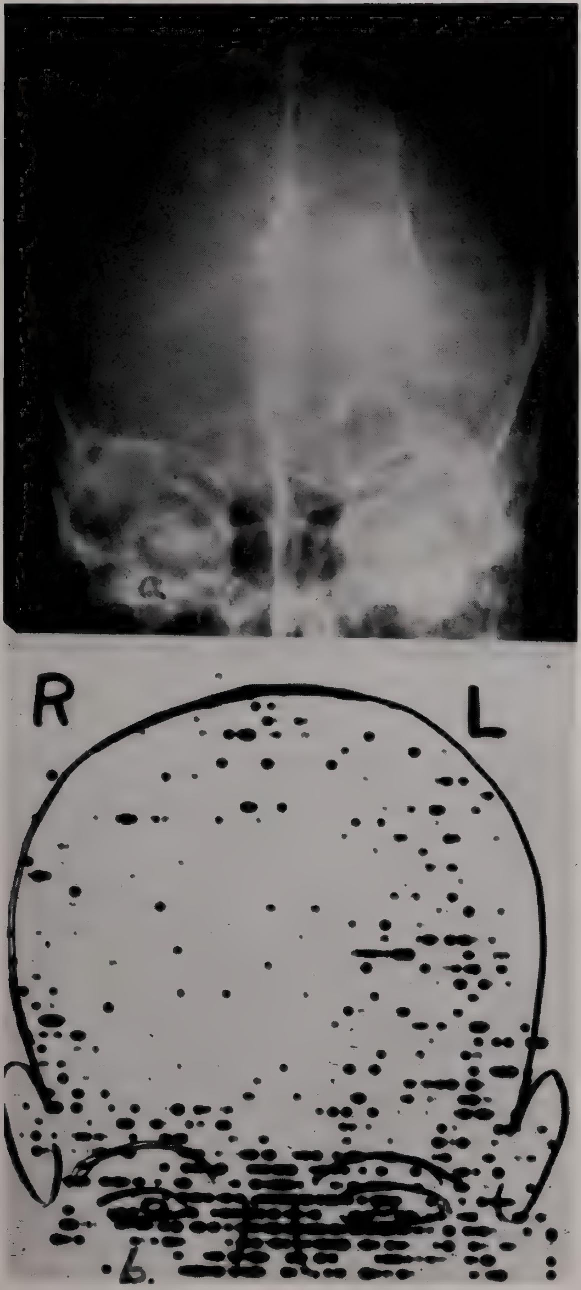

Fig. 9 — Large left frontal subdural hematoma. (a) Demonstrated by venous phase of left carotid angiogram. (b) Demonstrated by frontal projection of brain scan.

Discussion

Of the 45 primary brain tumors encountered in this series, approximately 85% revealed a positive brain scan. About 80% of the metastatic brain tumors revealed a positive scan. We encountered 30 positive scans of non-neoplastic lesions, with slightly more than ½ of these occurring in patients with cerebral vascular accidents.

Ten percent (44) of the brain scans were indeterminate.[8] In these cases we often noted moderately increased activity in basilar areas of the skull where adequate resolution of the lesion could not be obtained due to the normal activity found in areas of overly-

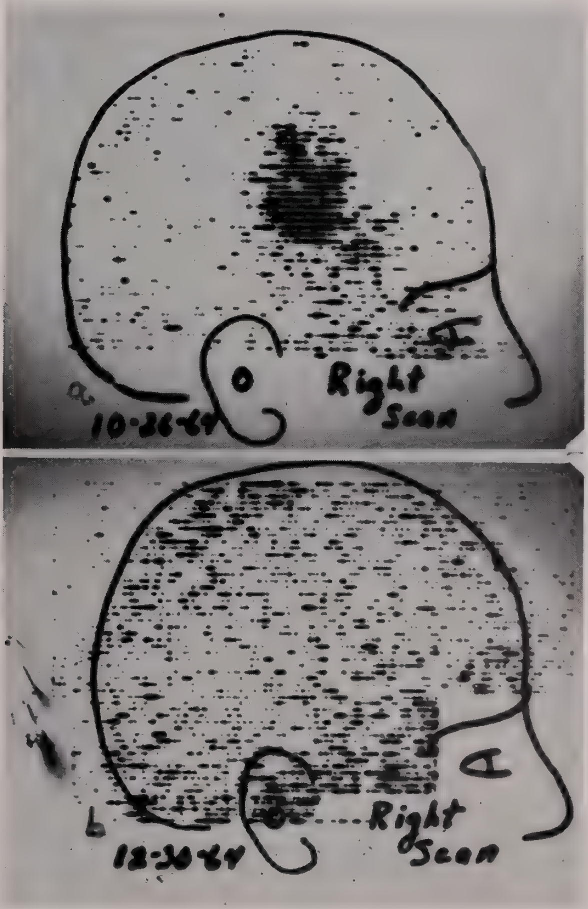

Fig. 10 — (a) Positive brain scan due to right middle cerebral artery occlusion. (b) Clearing of positive scan in same patient approximately two months later.

ing temporal or occipital musculature. Several of these cases of increased basal activity occurred in patients with extension of nasopharyngeal carcinomas to the brain. In others, slight areas of increased activity were noted, but a definitive impression could not be made either because the appropriate side of the brain had not been scanned or because needed additional projections had not been obtained. Another small group of scans was considered indeterminate because scanning had been performed at 24 hours only, with a total activity not great enough for reliable interpretation. A few cases showed slightly increased activity in areas of post-surgical cranial defects or soft tissue abnormalities overlying the skull and related to trauma or infection. With improved techniques and experience we believe this indeterminate group can be significantly reduced. However, even with the best technique, scans of questionable significance will be obtained, and experience indicates that these should be considered normal to avoid any danger of "over-calling".

Summary

Experience gained in the performance of 432 brain scans reveals that a high percentage of brain tumors can be detected and localized quite effectively by this procedure. The procedure has essentially no morbidity or adverse reactions. Brain tumors have been detected by this procedure when other methods have failed. In cases of metastatic brain tumors, the brain scan is often the only necessary special diagnostic procedure. In all cases of suspected brain tumor, brain scanning is a valuable adjunctive diagnostic procedure and, when possible, because of its low morbidity, brain scanning should be the first special diagnostic procedure attempted.

Acknowledgments

We wish to acknowledge with thanks the technical assistance of Mrs. Lucille Gomez, Miss Pearl Varian, Miss Norma Constantino and Mr. John Collis.

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The Tobacco Tyrant

The American Cancer Society considers the physician to be the key figure in reducing deaths caused by cigarette smoking.

The Society's Board of Directors urged physicians to recognize the need for stopping smoking as an example to patients and teenagers. The doctors were called upon to participate with their professional organizations in attempting to reduce cigarette smoking and "personally to instruct those in their care about the health hazards of cigarette smoking."

The American Cancer Society also asked that the physicians devote time to telling young people about the dangers of cigarettes with "particular emphasis on the difficulties of breaking the cigarette smoking habit, once it is firmly established."

Chronic Ulcerative Colitis in Children

Reevaluation of Management*

HUGH B. LYNN, M.D.**
Rochester, Minnesota

TRADITIONALLY, MANAGEMENT of a case of chronic ulcerative colitis in childhood has been left to the gastroenterologist who treats adult cases. The line of reasoning apparently has been that chronic ulcerative colitis is a disease children must live through until after adolescence and maturity. Also, in all too many cases the nonintestinal symptomatology has clouded the true diagnosis and has been the focal point of the family's concern over a prolonged period of insidious progression of the disease.

Everyone is aware of the intermittency of chronic ulcerative colitis and of the possibility that each episode may be the final one leading to recovery. However, review of the cases arising in childhood (if not diagnosed in childhood) leads to grave concern that this disease is far from being as simple as might be hoped. The earlier the onset and the more persistent or frequently recurring the symptoms, the grimmer the outlook appears to be. As pointed out by Michener and associates,[1] cancer is a real threat. Perforation, toxic megacolon, and crippling arthritis are some of the obvious hazards. Failure to grow, mature, and enjoy living are less of a concern, statistically, but are very real considerations. Even when surgery has been recommended and consent granted, the operation undertaken has often been the one most likely to be acceptable to the parents and the family physician, rather than the one the surgeon and the pathologist sincerely believe is most likely to effect a cure.

It is my belief that any patient with chronic ulcerative colitis which is truly disabling for any prolonged period (in some cases as short a period as six months) and which shows advanced roentgenographic and proctoscopic changes may be a candidate for surgery. I am well aware that very few parents are going to agree to surgery after the first six months without adequate counsel from a qualified pediatrician or internist. Simply on the basis of the child's "being too young," the possibility of surgery is summarily dismissed in most consultations with the family. The possibility of cancer and, what is much more of a concern, the probability of death from that cancer once it arises, is glossed over as too harsh for parents' ears when the alternative is permanent ileostomy and total colectomy. Having watched preadolescent children adjust to an ileostomy (one seven-year-old refers to his as "Cyclops") and having watched them gain weight, grow in stature, participate in the athletic and social events of their schools, and very definitely discover the opposite sex, I am completely unwilling to shudder and cringe at the thought of an ileostomy in a child.

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*Read at the meeting of the Minnesota Surgical Society, Duluth, July 16, 1965.

**Mayo Clinic and Mayo Foundation: Section of Pediatric Surgery.

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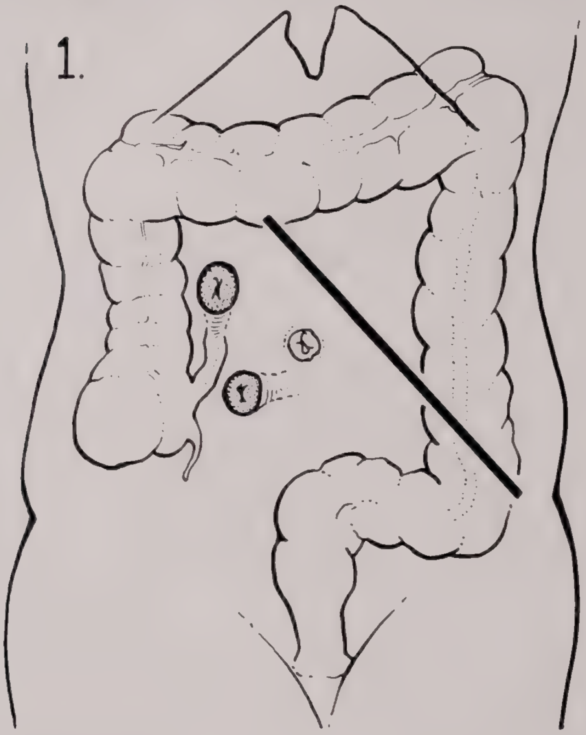

Certainly statistics indicate that the life expectancy is cut to approximately 20 years in more than 40% of these cases when the disease has its onset in childhood. In this era of increased and increasing longevity, 20 years is a very short time.

In the event that a surgeon is invited to consult on a child with chronic ulcerative colitis for other than profuse hemorrhage, toxic megacolon, perforation, and abscess formation, or complete wasting with chronic blood loss, decubitus ulcerations, or carcinoma (or more than one of these), various procedures are available that are recommended by many authorities. As I have suggested, a major portion of the surgery in childhood is of an emergency nature, and this is unfortunate.

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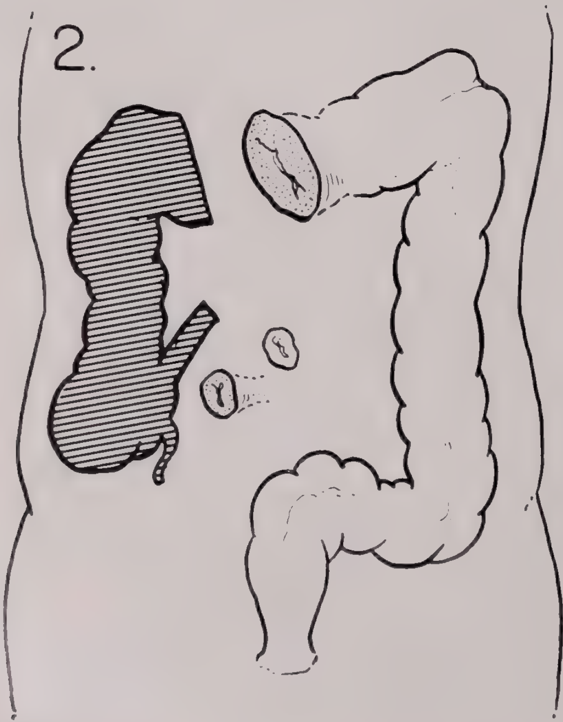

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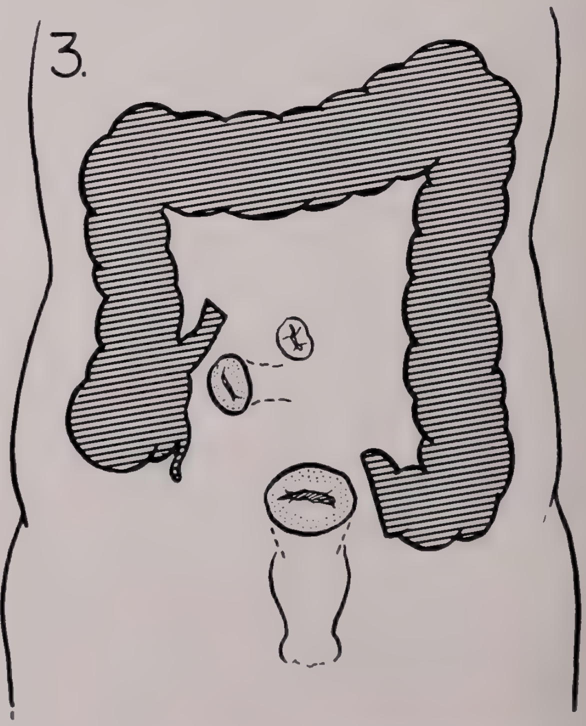


Emergency Procedures

Double-barreled Ileostomy

The simplest possible operation in a patient in extremis is a double-barreled ileostomy (Figure 1). This is seldom successful in the fulminating cases and is rarely indicated in any patient who can stand anything more extensive. The disease has shown little or no abatement in my experience.

Ileostomy and Partial Resection

Even in desperately ill patients, an ileostomy can usually be accompanied by resection of terminal ileum, cecum, ascending colon, and at least part of the transverse colon (Figure 2). When possible, the removal of more colon is desirable. This is a more desirable procedure if only to eliminate later surgery in the right lower quadrant should the patient survive and the ileostomy be permanent.

Extensive Resection with Temporary Fistula

Even in the emergency cases it is beneficial to remove as much diseased bowel as possible. A resection as extensive as the patient can reasonably stand is the objective. This will vary with the circumstances and the surgeon. The rectosigmoid can be brought out as a mucous fistula below the incision when the patient's condition does not warrant total removal or turning in of the stump. This fistula can be excised at a later date but should *not* be left indefinitely (Figure 3). In our series carcinoma appeared in a defunctionalized stump 17 years after permanent ileostomy.

Elective Procedures

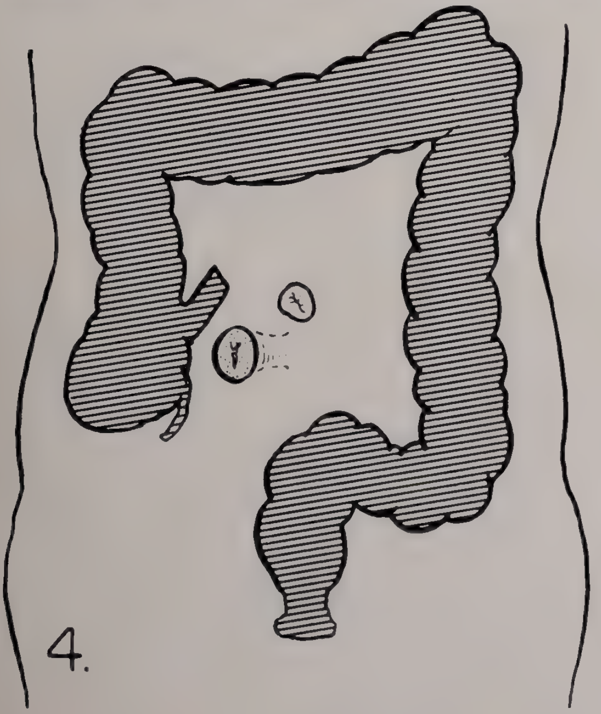
Eventually it is hoped that good surgical results and poor medical results with pediatric cases will lead to a change in attitude on the part of referring physicians and parents. This change can be advanced only by vigorous efforts on the part of surgeons to come to grips with the issue.

Ileostomy and Total Colectomy

If there is obvious acute involvement of the rectum by the ulcerative process, little is to be gained (and much may be lost) by temporizing. A permanent ileostomy and total colectomy including the anus and rectum is indicated (Figure 4).

Resection with Saving the Rectum

In patients with moderate rectal involvement, there are possibly some advantages in saving the rectum for future reanastomosis. These advantages seem to me to be more theoretical than real, but the psychologic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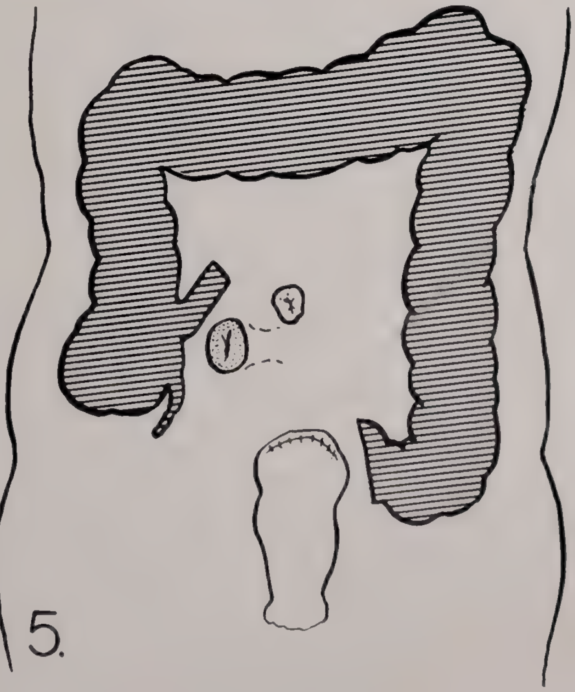
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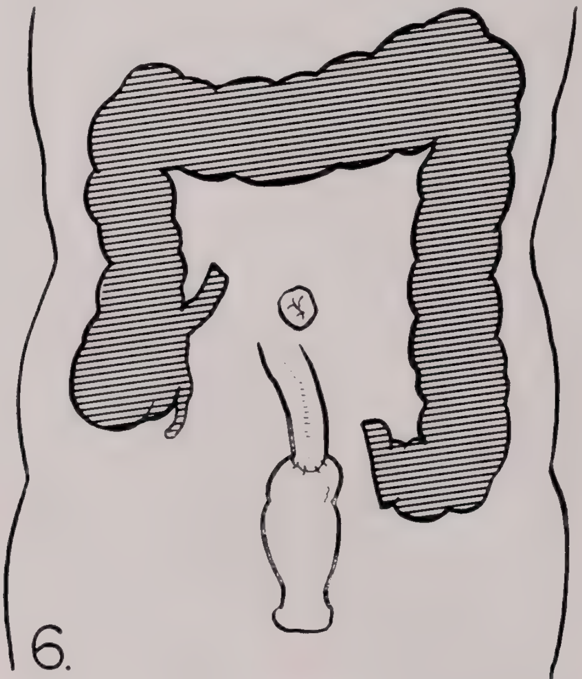
value for the parents may justify it (Figure 5).

Anastomosis of Ileum to Rectum

When proctoscopy shows minimal involvement of the rectum, the idea of removing the colon and anastomosing the ileum to the rectum seems attractive (Fig. 6), at least to the parents and the referring physician. In my hands, this has been a fairly unsatisfactory substitute. The hazards of fistula, abscess, and obstruction seem to be unusually high. However, in one patient who returned for removal of the rectum and permanent ileostomy, at the insistence of the parents, the mother remarked that they could not have considered a permanent ileostomy 10 months before.



6.

Comments

In the past year I find I have employed all six operations, so that I cannot be too dogmatic about the choice of the elective procedures which have all too often been dictated by the emotions of the parents and the referring physician. I believe it is time that we, as intelligent physicians, make a more aggressive attack on this problem, both in the emergencies and in the elective cases, in order that the patient, the referring physician, and the parents can be adequately prepared both physically and emotionally for permanent ileostomy and total colectomy.

At this point it must be acknowledged that an ileostomy is not without complications and problems. In my own experience my ileostomy patients have actually had less difficulty with prolapse, stenosis, and retraction than have my colostomy patients.

Selecting the Site for Ileostomy

Whenever possible, the location of the site for ileostomy is now selected before operation by fitting the appliance of choice and allowing the patient to be active about the ward and making all his usual moves, so that it is possible to mark the position where it is most comfortable and where it is most likely to end up after the patient has climbed stairs, sat down and arisen from a chair, gotten in and out of bed, and so on. This usually results in placement of the stoma at a higher level with relation to the umbilicus than has been our custom.

Psychiatric Therapy

Within the last year, I have seen a 14-year-old boy with ileostomy and subtotal colectomy lie curled up in bed with no interest in ever getting up and leaving the hospital (his rectosigmoid was left as a mucous fistula because of the emergency nature of the surgery for perforation and pelvic abscess). Our psychiatric section had recommended his transfer to the open psychiatric floor for prolonged therapy. However, a pretty little nine-year-old girl who had been well prepared by intelligent parents and had taken her permanent ileostomy in stride was prevailed on to visit with this boy. Two visits did the trick. The knowledge that he was not alone, that he was not completely mutilated and defeated, and that others with his condition were taking overnight hikes, going to parties, and having fun was all that he needed. In three days he was out of the hospital and at home. Since then he has returned for the removal of the rectum and rectosigmoid. Everyone who knew him is impressed with the progress he has made in adjusting to his physical state and his relationship to an overly protective mother.

From many such experiences it would appear to me that children have an amazing and incomprehensible ability to adjust to their circumstances. Only parents and physicians who are revolted by the thought of an ileostomy could be so cruel and unreasonable as to permit a youngster to suffer years of disability and danger on the never-voiced hope that even if the malady does not clear up, perhaps ileostomy can be avoided until after the child's wedding and honeymoon. What an unfair and ridiculous way to view such a crippling disease

Summary

Chronic ulcerative colitis in childhood is a dangerous and dreaded disease. Palliation and temporizing during childhood in the hope of permitting normal growth and development are therefore deplored.

A strong plea is made for an earlier and more extensive surgical attack upon the diseased colon. An ileostomy is not too great a price to pay for freedom from such a horrible disease!

Reference

1. Michener, W. M., Gage, R. P., Sauer, W. G., and Stickler, G. B.: Prognosis of Chronic Ulcerative Colitis in Children. New Engl J Med 265:1075, 1961.

IT'S THE LAW

Doctor's License Suspended for Attempted Income Tax Evasion

The Board of Medical Examiners did not abuse its discretion in staying the revocation of a doctor's license for five years and placing him on probation during that period and in suspending his license for 180 days, where there was sufficient evidence to sustain its finding that he was guilty of unprofessional conduct in having been convicted, following a plea of *nolo contendere,* on two charges of attempting to evade payment of federal income taxes, which were offenses involving moral turpitude, a California intermediate appellate court ruled.

The doctor, who owned a hospital, had an arrangement with an insurance company to furnish medical and hospital services to Mexican workmen at a flat rate per month per laborer and an arrangement with a county to furnish medical and hospital services to people receiving Old Age Security. He exchanged the monthly checks he received from the insurance company and the county for cashier's checks, and the amount of those checks was not entered in the general income account kept by his bookkeeper from which his income tax returns were prepared. As the hospital needed money or the doctor needed money for living expenses, he would cash the cashier's checks. The doctor said that he followed this method to prevent his competitors from finding out how much income he received from the insurance company and the county.

The doctor contended that a conviction of a felony did not constitute unprofessional conduct unless the felony was one involving moral turpitude. The Board made a specific finding that the offenses of which the doctor was convicted involved moral turpitude. Although the doctor kept a record of the amounts received from the insurance company and the county in a place other than his regular income account, he did not tell the accountants that prepared his income tax returns about the income. There was sufficient evidence to support the inference that the doctor intentionally and for the purpose of personal gain filed false income tax returns and had thus been guilty of moral turpitude, the court said.

Morris v. Board of Medical Examiners, 41 Cal. Rptr. — Citation — March 15, 1965. 351 (Cal., Nov. 17, 1964)

Acid-Base and Serum Electrolyte Values

in Clinical Practice[*]

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THE PRECISE evaluation of acid-base balance requires the analysis of arterial blood for pH, partial pressure of carbon dioxide (pCO_2) and true (arterial) plasma bicarbonate concentration ($[HCO_3^-]$).[1] Only in rare instances are these determinations performed routinely in the clinical laboratory. The published acid-base data indicate that the measurement of these three variables continues to be confined primarily to research laboratories.

The theoretical aspects of acid-base balance, especially the conceptual and terminological contradictions existing in this field, have been repeatedly discussed in the clinical

TABLE I

Outline of the Nomenclature and the Diagnostic Criteria on Which it is Based

	pH	pCO_2 mmHg	$[HCO_3^-]$ mM/L	$[HCO_3^-]_{7.40}$ mM/L
Mixed Metabolic-Respiratory Alkalosis	I	R	I-N-R	I
Mixed Metabolic-Respiratory Acidosis	R	I	I-N-R	R
Respiratory Acidosis — Uncompensated	R	I	I	N
Respiratory Alkalosis — Uncompensated	I	R	R	N
Respiratory Acidosis — Partially Compensated	R	I	I	I
Respiratory Alkalosis — Partially Compensated	I	R	R	R
Respiratory Acidosis — Completely Compensated	N	I	I	I
Respiratory Alkalosis — Completely Compensated	N	R	R	R
Respiratory Acidosis — Completely Compensated-Alkaline pH	I	I	I	I
Metabolic Alkalosis	I	N	I	I
Metabolic Acidosis	R	R	R	R
Normal	N	N	N	N
No: 66	7.40 ±.02	40.5 ±2.2	24.4 ±1.1	24.4 ±1.1

N — Normal; R — Reduced; I — Increased.

R and I apply to change from the listed normal values. The grouping of the various disturbances is arbitrary and demonstrates the contrast in the four variables.

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TABLE 2

Patient	A	B
Hemoglobin gm%	7.5	19.5
pH	7.20	7.20
pCO_2 mmHg	70.0	70.0
$[HCO_3^-]$ mM/L	26.5	26.5
$[HCO_3^-]_{7.40}$ mM/L	23.1	18.6

Two patients with identical pH, pCO_2 and $[HCO_3^-]$ values which indicate severe respiratory acidosis. The $[HCO_3^-]_{7.40}$ value in patient A is within normal limits and he has an uncompensated respiratory acidosis. The $[HCO_3^-]_{7.40}$ value in patient B is definitely reduced, indicating a bicarbonate deficit, i.e., a state of mixed respiratory-metabolic acidosis.

literature of the past decade.[2-7] This polemic, which through its clarification and redefinition of certain basic concepts has been most valuable, has also unintentionally made this field somewhat esoteric. It appears as if these theoretical discussions have at least temporarily overshadowed the practical aspects of these measurements in clinical medicine.

The use of these measurements under clinical conditions has been greatly facilitated by the replacement of cumbersome methods with techniques which are well suited for use in a clinical laboratory. The clinical manifestations of acid-base disturbances have been incompletely defined, and concise criteria for the existence of a particular disturbance are generally lacking. The use of these measurements not only as a diagnostic tool but specifically as a therapeutic guide or a prognostic aid in clinical practice is only occasionally recorded.[8,9]

The analysis of an unselected sample of acid-base determinations performed in a routine clinical laboratory is the subject of this report. The simplicity of the technical procedure from the arterial puncture to the actual analysis is emphasized, as well as the usefulness of the direct measurement and the lack of validity of indirect estimates from serum electrolytes.

Method of Study

Materials

The materials for this study consisted of the clinical records of 212 patients in whom a total of 396 acid-base determinations were performed by the clinical laboratories of the Minneapolis Veterans Hospital during an arbitrarily selected time interval of six months (October 1963 to March 1964).

Methods

The acid-base determinations were performed at 38° C on anaerobic whole arterial blood using the Radiometer Astrup Microequipment; the pCO_2 and $[HCO_3^-]$ were obtained by the Astrup interpolation technique.[10] The values were corrected to the patient's temperature if it differed from 38° C, using the correction factors previously reported from this laboratory.[11] The actual $[HCO_3^-]$ were corrected for the buffering effect of whole blood to pH 7.40; these values are designated by the symbol $[HCO_3^-]_{7.40}$. When using the Astrup micro-equilibration technique, the intersect of the equilibration curve and pH value 7.40 is the $[HCO_3^-]_{7.40}$. The $[HCO_3^-]_{7.40}$ may also be calculated from an equation proposed by Van Slyke.[12] "Standard bicarbonate," proposed by Astrup,[10] differs from the $[HCO_3^-]_{7.40}$ in that it represents a correction of the actual bicarbonate concentration to a pCO_2 of 40 mmHg instead of to a pH of 7.40.

Sodium and potassium were determined by flame photometry, chloride by a modified method of Schales and Schales,[13] and CO_2 combining power by the method of Van Slyke.[14]

The Collection of Blood

According to an established routine at this institution, the arterial blood is obtained by the Junior house staff. The brachial artery is the most common site of puncture (80%), the femoral artery the next. The equipment used is a standard 10-cc. syringe and a 20-gauge disposable needle. The syringe is prepared by wetting the walls with heparin and filling the dead space of the syringe and the needle with heparin solution. Anesthesia of skin produced by injection (25-gauge needle) of 1% procaine solution minimizes a ventilatory response to the puncture. After the artery is entered percutaneously the syringe is allowed to fill under the influence of the blood pressure. Using this technique, there is as a rule no visible air bubble present; however, if one is present, it is expelled immediately after a specimen is obtained. The needle is left on the syringe after completion of the puncture and inserted into a rubber stopper; the entire syringe is immediately iced, and determinations are carried out as rapidly as possible (within one hour). Manual pressure is applied over the area of puncture for a minimum of eight minutes.

Interpretation of Values

The laboratory report contains the following values:

pH
pCO_2 (partial pressure of carbon dioxide)
$[HCO_3^-]$ (true plasma bicarbonate)
$[HCO_3^-]_{7.40}$ (true plasma bicarbonate corrected for the buffering effect of whole blood to pH 7.40)

The nomenclature which is in use at this institution is listed in Table 1. The diagnostic criteria are based on the four variables reported by the laboratory. Although the distinct separation of the various diagnostic categories is made possible by the $[HCO_3^-]_{7.40}$ value, this is only a partial justification for its use. The use of $[HCO_3^-]_{7.40}$ allows one to quantify changes in bicarbonate concentration which are in excess of that produced by blood-buffer shifts in response to variation in pCO_2. This is demonstrated by contrasting the values from two patients listed in Table 2, both of whom had severe obstructive pulmonary emphysema. Patient A was anemic; patient B had elevation of blood hemoglobin. Since the pH, pCO_2 and $[HCO_3^-]$ values are identical in both patients it may be concluded that their acid-base disturbance is of identical severity. However, the $[HCO_3^-]_{7.40}$ value in patient B shows that he has an absolute bicarbonate deficit and therefore a mixed respiratory-metabolic acidosis; the disturbance in patient A is an uncompensated respiratory acidosis.

There were occasional values which could be interpreted only with knowledge of the patients' clinical states. Examples of such acid-base values in two patients are shown

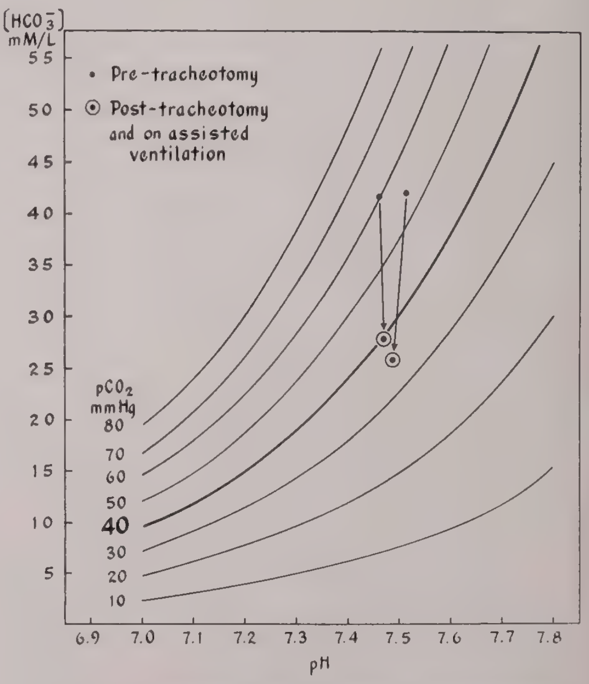

Fig. 1 — Note the nearly normal post-tracheotomy acid-base values, which are possible only while the emphysematous patients are on assisted ventilation.

on a bicarbonate-pH diagram in Figure 1. The post-tracheotomy values are nearly normal. These values were possible only because of the assisted ventilation.

Results

Of the 396 acid-base determinations, 354 were performed on blood samples obtained by direct arterial puncture. In 42 instances the blood was obtained through arterial cannulas during extracorporeal circulation* in open-heart surgery or renal hemodialysis.

The Reason for Acid-Base Studies

Abnormal respiration was the clinical sign most commonly used as an indication for an acid-base evaluation (132 instances); the presence of vomiting and/or diarrhea was the next most frequently used clinical indication (56 instances). An established routine during open-heart surgery and renal hemodialysis accounted for 49 determinations.

Predictability of Acid-Base Findings

The existence of a specific type of acid-base disturbance was predictable on clinical grounds in 166 instances (42%); however, in 128 of these an abnormal serum electrolyte pattern was equally suggestive. In an additional 57 cases (14%) a combination of clinical findings and serum electrolyte patterns was indicative of a specific type of acid-base disturbance. In 124 (31%) the findings could not be predicted from available clinical information or serum electrolyte pattern. However, although the type of acid-base disturbance was predictable in 223 instances, there was not a single case in which the precise acid-base values could be estimated from the clinical serum electrolyte findings.

Clinical States and Acid-Base Balance

No specific acid-base abnormality was exclusively associated with a single clinical state. The distribution of acid-base findings among broad categories of clinical abnormalities is shown in Table 3. However, among the various acid-base disturbances certain specific clinical states were predominant: obstructive pulmonary emphysema in respiratory acidosis, pyloric obstruction and thiazide administration in metabolic alkalosis, chronic glomerulonephritis in metabolic acidosis and postoperative state after major surgical procedures in mixed metabolic respiratory acidosis.

Lack of Association Between Acid-Base and Serum Electrolyte Values

The distribution of the 396 acid-base values is shown on a bicarbonate-pH diagram in Figure 2. The shape of the areas occupied by the various types of disturbances is formed by a line connecting the extreme points in each group. In 187 instances, serum electrolytes were determined on the day of the acid-base determination; the distribution of the 187 acid-base determinations is shown in

TABLE 3
The Distribution of the Various Acid-Base Disturbances Among Broad Categories of Clinical States

	Respiratory Acidosis	Metabolic Alkalosis	Normal	Respiratory Alkalosis	Metabolic Acidosis	Mixed Respiratory-Metabolic Acidosis
Lung Disease	78	6	4	9	0	4
Heart Disease	7	20	10	18	2	0
Gastrointestinal Disease	0	11	4	4	1	0
Liver Disease	3	11	2	12	1	1
Kidney Disease	1	1	3	6	13	3
Miscellaneous	1	10	5	22	7	0
Open-Heart Surgery including pre and post op.	9	3	4	23	11	12
Renal Hemodialysis including pre, post and between dialysis	2	2	2	11	3	0
Post Major Surgery	4	6	1	14	4	5
Total	105	70	35	119	42	25

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*See Test Your Word Score Page 447.

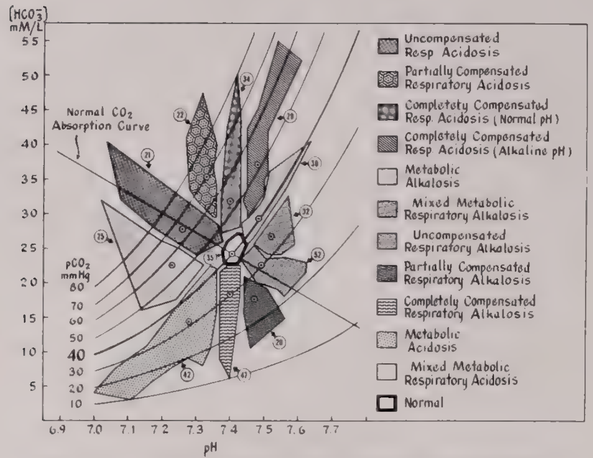

Fig. 2 — The shape of the areas representing the various acid-base disturbances was formed by a line connecting the extreme points in a given group. The round circle within each area is the mean value and the figures are the number of determinations in each group.

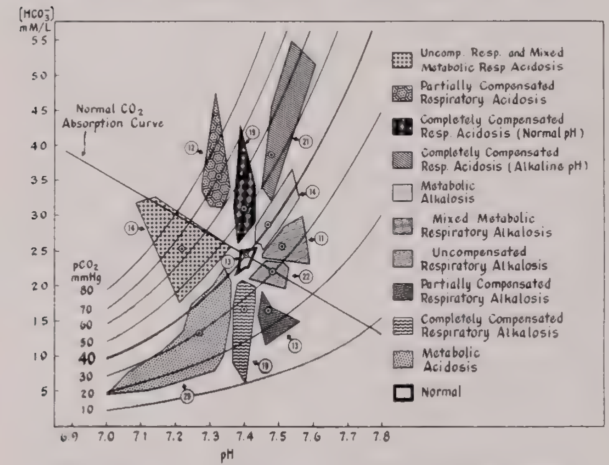

Fig. 3 — In this group of 187 acid-base measurements serum electrolytes (Fig. 4) were determined on the same day. Note that because of smaller number, two groups, mixed metabolic-respiratory acidosis and uncompensated respiratory acidosis, are combined.

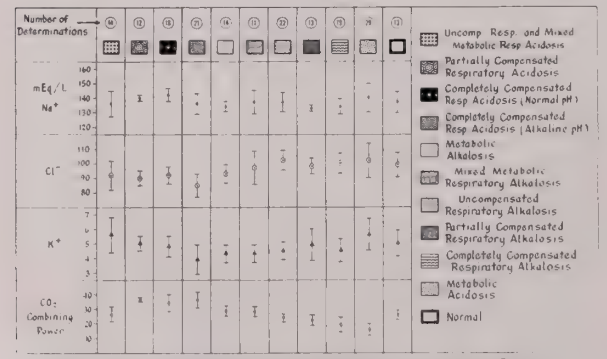

Fig. 4 — The mean and range of serum electrolyte concentrations determined on the same day as the acid-base measurements. The distribution of the corresponding acid-base values is shown in Fig. 3.

Figure 3, and the serum electrolyte concentrations corresponding to each acid-base group are shown in Figure 4. Table 4 lists the mean values and ranges for the data shown in Figures 2 and 3. The two groups, mixed respiratory-metabolic acidosis and uncompensated respiratory acidosis, are combined.

These data fail to reveal a serum electrolyte pattern characteristic of a specific type of acid-base disturbance. In general the CO_2 combining power appeared to parallel the plasma bicarbonate concentration; however, in many instances this determination proved to be most misleading. The serum potassium was elevated in most but not all instances of acidosis and was frequently reduced in the presence of alkalosis. This tendency to an inverse relationship between potassium concentration and pH value was not related to the primary nature of the acid-base disturbance, i.e., whether respiratory or metabolic. A normal serum electrolyte pattern was not uncommon in each specific type of acid-base disturbance. Attention is called to the occurrence of abnormal serum electrolytes among the patients whose acid-base values were normal.

Discussion

At present, percutaneous arterial punctures for acid-base analyses are being performed at this hospital at an annual rate exceeding one thousand, most of them by the Junior house staff using the described technique. The absence of morbidity in several thousand arterial punctures demonstrates the safety of the procedure. We believe that the application of manual pressure over the puncture area for a minimum of eight minutes is a major factor in the prevention of leakage.

The lack of specificity of serum electrolyte patterns in the diagnosis of acid-base disturbances is self-evident from the data presented. Although the type of acid-base disturbance was predictable in some patients, the assessment of its severity was usually not possible on the basis of the serum electrolytes. Measurement of severity is basic to the selection of proper corrective measures, the intensity with which these are applied, and the evaluation of the response.

Two examples of recovery from a severe disturbance in acid-base balance not reflected in serum electrolytes are shown in Table 5. Patient A was a 67-year-old man admitted for the first time in severe respiratory distress with clinical findings of severe obstructive pulmonary emphysema and decompensated cor pulmonale. Patient B was a 40-year-old man with renal amyloidosis secondary to extensive tuberculosis. On admission this patient was hypotensive, disoriented, and hyperventilating severely. Both patients recovered; in both therapy was guided by serial acid-base measurements.

Quantitative approaches to therapy of disturbances in acid-base balance have been proposed.[15,16] These are applicable primarily to abnormalities in which there is a bicarbonate deficit, and are essentially guides for the replacement of an existing deficit as calculated from the plasma values. The desirability of therapy appropriate to the needs

TABLE 4
The Mean Values and the Range of 187 Acid-Base and Serum Electrolyte Measurements

	No.		pH	pCO_2 mmHg	$[HCO_3^-]$ mM/L	$[HCO_3^-]_{7.40}$ mM/L	Na mEq/L	K mEq/L	Cl mEq/L	CO_2 Comb. Power mEq/L
Uncomp. Resp. Acidosis and Mixed Metabolic-Respiratory Acidosis	14	Mean	7.22	65.1	25.1	20.5	136	5.6	92	26.4
		Range	7.08-7.36	46.0-110.0	17.8-32.7	11.0-25.0	118-147	3.7-7.4	73-106	18 5-32 5
Partially Comp. Resp. Acidosis	12	Mean	7.33	69.7	35.3	33.2	140	5.0	90	36.7
		Range	7.28-7.36	59.0-95.0	31.2-47.5	27.4-44.9	136-144	4.3-6.2	78-96	33.4-44.9
Completely Comp. Resp. Acidosis (Normal pH)	19	Mean	7.40	51.6	30.9	30.9	142	4.8	92	33.9
		Range	7.37-7.43	44.5-73.0	26.1-42.9	26.1-50.2	135-152	3.6-6.2	74-102	23.6-44.9
Completely Comp. Resp. Acidosis (Alkaline pH)	21	Mean	7.48	52.9	38.5	40.5	136	3.9	85	36.3
		Range	7.45-7.61	44.5-66.0	32.1-54.7	31.3-58.6	123-154	2.2-5.8	73-98	30.8-45.7
Metabolic Alkalosis	14	Mean	7.47	40.1	28.6	30.3	134	4.3	93	28.7
		Range	7.43-7.56	37.0-45.0	25.1-36.4	27.1-39.1	128-141	3.2-5.1	82-105	23.2-34.2
Mixed Metabolic Resp. Alkalosis	14	Mean	7.51	32.8	25.6	28.8	136	4.4	97	27.1
		Range	7.45-7.59	29.8-36.7	22.9-28.4	26.7-33.0	119-151	3.1-6.1	66-110	21.9-35.1
Uncomp. Resp Alkalosis	22	Mean	7.48	30.4	21.9	23.5	138	4.4	103	24.2
		Range	7.41-7.53	27.2-36.3	19.5-23.8	21.5-26.5	126-150	3.6-5.2	88-125	19.8-36.8
Partially Comp. Resp. Alkalosis	12	Mean	7.47	24.4	16.4	18.0	133	4.9	97	21.9
		Range	7.44-7.56	17.0-29.0	11.6-19.5	14.0-20.8	123-141	3.2-7.1	88-107	12.5-35.5
Completely Comp. Resp. Alkalosis	20	Mean	7.40	27.4	16.5	16.5	133	4.6	100	19.2
		Range	7.37-7.43	10.0-35.6	6.3-20.4	6.3-20.7	120-144	2.9-6.2	85-113	9.1-24.4
Metabolic Acidosis	29	Mean	7.27	27.6	13.2	10.5	140	5.6	102	15.1
		Range	7.00-7.36	16.4-41.0	4.6-22.5	0.0-19.8	126-184	3.8-9.0	86-149	7.0-25.3
Normal	13	Mean	7.40	40.0	24.2	24.2	137	5.0	99	26.0
		Range	7.37-7.43	37.0-43.0	21.5-26.0	21.5-26.0	121-150	3.6-6.8	84-105	19.3-30.0

TABLE 5
Serial Acid-Base and Serum Electrolyte Measurements During Recovery from Respiratory Acidosis (Patient A) and Metabolic Acidosis (Patient B)

Patient	Date	pH	pCO_2 mmHg	$[HCO_3^-]$ mM/L	$[HCO_3^-]_{7.40}$ mM/L	Na mEq/L	K mEq/L	Cl mEq/L	CO_2 Comp. Power
A	3-12-64	7.28	73.0	33.4	28.9	139.0	5.8	93	30.8
	3-16-64	7.30	66.0	31.5	28.0	140.0	5.2	91	33.4
	3-20-64	7.35	61.4	32.9	31.7	138.0	5.2	93	32.0
	3-23-64	7.41	51.2	31.5	31.8	139.0	5.3	90	30.0
B	11-15-63 A.M.	7.06	27.8	7.7	5.5	140	6.0	118	8.3
	11-15-63 P.M.	7.20	29.6	11.2	8.0	—	—	—	—
	11-16-63	7.31	29.7	14.2	12.1	—	—	—	—
	11-18-63	7.32	44.6	22.2	20.7	143	5.2	109	15.9

The changes in the serum electrolytes do not reflect the progressive reduction in pCo_2 in patient A and the marked improvement in the metabolic acidosis of Patient B.

of the individual patient is self-evident. The data available in the literature are an inadequate basis for such ideal therapy, indicating a definite need for additional studies in this area.

Little is known at present about the effect that a disturbance of hydrogen-ion metabolism may have upon the course of a given clinical entity. It is generally stated that the range of blood pH compatible with life is 6.80 to 7.80;[17] however, the mechanisms through which values outside this range become incompatible with life are obscure. The need for extensive clinical studies in order to define any correlations which may exist between clinical symptomatology and the underlying disturbance in hydrogen-ion metabolism cannot be overemphasized.

The occurrence of disturbances in hydrogen-ion metabolism in a variety of unrelated clinical states has been demonstrated in this study. The rapidity with which an acid-base disturbance may develop is not widely recognized. On many occasions we have observed a reduction in bicarbonate concentration exceeding 50% of the original value during an interval of several hours. A spontaneous gain in bicarbonate concentration of similar magnitude has also occurred rapidly, but with less frequency. Changes in ventilation are followed by an almost instantaneous change in pCO_2 and therefore rapidly reflected in the acid-base determinations.

Abnormal respiration (hypo-or hyperventilation) is the clinical manifestation which most clearly indicates the presence of an acid-base disturbance. The respiratory abnormality may occur as a consequence of such disturbance or may be its cause. It should be noted that approximately 90% of the abnormal acid-base values observed were associated with an abnormal pCO_2. Other clinical manifestations which were thought related to the existing acid-base disturbance were twelve instances of tetany (overt clinical tetany three, positive Chvostek's sign nine) in patients with primary respiratory or metabolic alkalosis, and seven instances of hypotension responsive to correction of acidosis.

Almost two thirds of the cases of chronic respiratory acidosis in patients with obstructive pulmonary emphysema were completely compensated as indicated by a normal or alkaline pH. This finding is in conflict with a suggestion advanced in the literature[6] that complete compensation does not occur. Instances of alkaline pH in such patients have been reported previously.[18] The hospital mortality rates among these patients with pulmonary emphysema were of interest since they indicate the potential usefulness of the acid-base determinations as a prognostic aid. The mortality rate was 60% in the group with mixed respiratory-metabolic acidosis and uncompensated respiratory acidosis, 31% in the group with partially compensated respiratory acidosis, and 16% in the group with completely compensated respiratory acidosis (pH normal or alkaline).

As might be expected, the highest mortality, over 80%, was observed in patients with mixed respiratory-metabolic acidosis, since this disorder reflects the functional failure of the two organs primarily concerned with acid-base regulation, viz., the lungs and the kidneys. The occurrence of this disturbance in patients after major surgical procedures is a serious complication.

Summary

Abnormalities in the hydrogen-ion metabolism occur in a variety of unrelated clinical conditions, both medical and surgical. The specific type and the severity of an abnormality in hydrogen-ion metabolism cannot be accurately diagnosed from serum electrolytes and require the determination of pH, pCO_2 and bicarbonate concentration, the latter performed on arterial blood.

Arterial puncture is not a difficult technical procedure, and the diagnostic precision of acid-base determinations from arterial blood make it a very desirable clinical test.

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Congenital Cystic Dilatation of the Common Bile Duct

Preoperative Diagnosis by Intravenous Cholangiogram.

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Eloise, Michigan

THE DIAGNOSIS OF congenital cystic dilatation of the common bile duct has been considered preoperatively in only 30% of the 403 cases reported in the world literature.[1,2,3] The mortality of this disease, when multiple operations have been performed, is 69% and only 9% with primary anastomosis.[4] Because most surgeons encounter congenital cystic dilatation of the common duct without previous personal experience and without warning,[5] it is obvious that all surgeons who operate upon the biliary tract should be familiar with the treatment of these cysts.

Vater, in 1723, first reported a congenital cyst of the extrahepatic biliary tree. Judd and Green found one in every 17,381 cases of biliary tract surgery. Smith noted two cases in 757,000 hospital admissions. Alonso found 403 cases in the world literature, constituting an average of one per 250,000 hospital admissions.

These cysts have been reported in stillborn infants and in persons of all ages up to 65.[7]

A well defined classification of choledochal cysts has not been established. Though Alonzo referred to cystic dilatation of the common bile duct as being the most common, he observed three cases of congenital diverticula and four of congenital choledochocele within the duodenal wall. Gross,[4] in describing his cases, referred to congenital weakness of a portion of the common bile duct associated with distal obstruction, which could be either congenital or acquired.[5]

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Clinical Symptoms

The classic triad of abdominal pain, mass, and jaundice was present in 20 to 60 per cent of the reported cases.[5] Children most often have obstruction with jaundice, whereas adults usually have pain or pancreatitis.

The differential diagnosis[4,5] includes echinococcal cysts of the liver which remain stationary in size, are rarely painful, and can be confirmed by eosinophilia and complement fixation tests; cholelithiasis in children is rare unless hemolytic disease is present; abdominal neoplasms are stationary in size, solid, irregular, and without jaundice; congenital atresia of the bile ducts becomes evident in neonates; congenital cysts of the liver are usually small, multiple and associated with cystic disease, and pancreatic cysts are more to the left of the abdomen.

X-ray Findings

Flat plates of the abdomen may reveal a right upper quadrant mass displacing the bowel, and barium in the stomach may show the duodenum displaced inferiorly and to the left.

An oral cholecystogram frequently shows nonvisualization, whereas intravenous cholangiograms may be diagnostic if the serum bilirubin is normal. The terminal common duct is usually narrowed, but there is marked cystic dilatation with normal hepatic radicals. The cyst may be confused with the normal gallbladder, but the pointed end of the cyst adjacent to the ampulla of Vater suggests that the abnormality is not a gallbladder. Jesseman[8] warns that one may be misled by the presence of contrast media in the upper portion of the duodenum; therefore, concurrent intravenous cholangiography and upper gastrointestinal x-rays are essential to rule out this possibility.

Treatment

Partial or complete excision, first done by McWhorter in 1922, is especially suitable for a diverticulum type of choledochal cyst, having the lowest postoperative morbidity but a high operative mortality ranging up to 50 per cent.[5]

Roux-en-Y cysto-jejunostomy

Ferris[3] and Maingot,[9] because of the low incidence of postoperative cholangitis, prefer the Roux-en-Y procedure; Ravitch[10] rec-

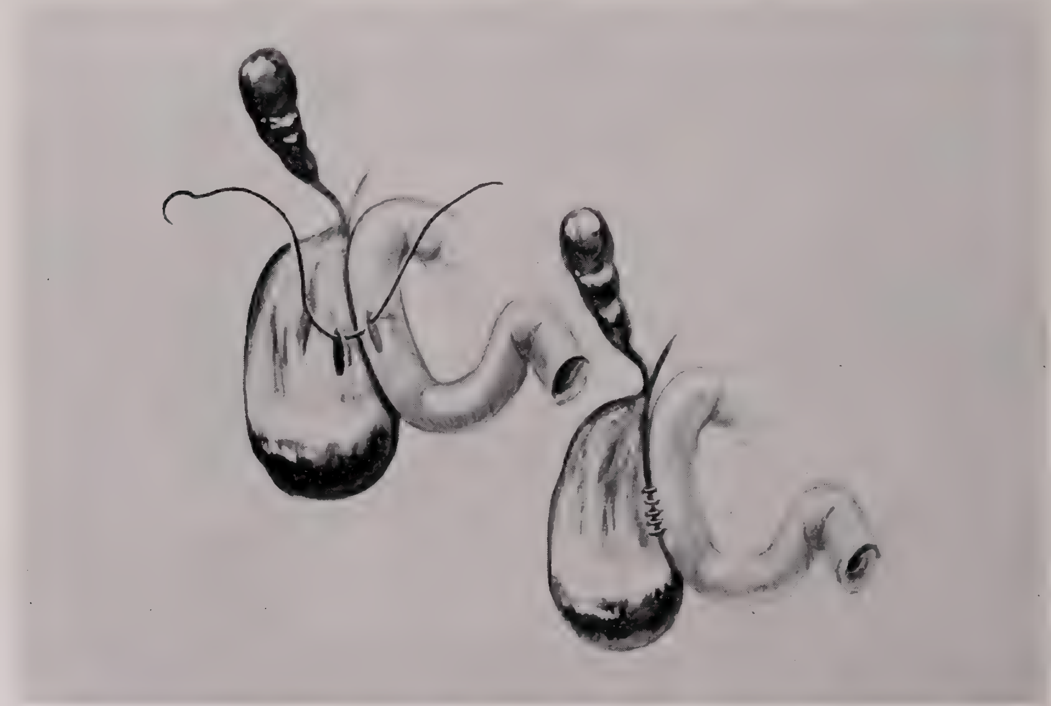

Fig. 1 — Artist's view of choledococysto-duodenostomy in a four-year-old child. (The anastomosis was more dependent than illustrated).

ommends it as the treatment of choice in large cysts. Others advise concurrent excision of the redundant portion of the sac.

Cysto-gastrostomy

Excision of the cyst and replacement with a gastric tube pedicle is a unique procedure popularized by Heimlich,[11] having the advantage of the Roux-en-Y procedure; in addition, it reduces peptic ulceration by retaining the bile flow into the duodenum instead of the jejunum.

Other Procedures

A gallbladder bypass can be used if excessive adhesions are present near the cyst, and a choledochocele is best corrected by a simple incision into the duodenal wall. Choledochorraphy is an inadequate primary procedure because it fails to correct the common duct obstruction.

Cysto-duodenostomy

This procedure is best for *small* retroduodenal cysts in which the dependent portion of the cyst can be anastomosed to the duodenum (Figure 1). Numerous cases of postoperative occlusion of these anastomoses have been reported; up to 30 per cent of these patients have postoperative recurring pain, fever, or cholangitis. Despite this, Gross[4] and many other surgeons advise this procedure because it carries a low operative mortality.

All three of our cases were treated in this way.

Case Reports

Case 1

This four-year-old Negro presented herself with a two-week history of itching, yellow eyes, mild intermittent abdominal pain of two weeks duration, but no nausea or vomiting. Two previous episodes of "yellow eyes," when the child was two and three years old, were treated at home by her grandmother.

Physical examination showed an icteric child in no apparent distress. A tensely cystic abdominal mass extended four finger-breadths below the right costal margin. The stools were clay-colored. The hemoglobin was 12.4 grams and the leukocyte count was 9,350. The urine contained bile and the direct serum bilirubin was 8.4 mgm.% with a total of 11.4 mgm.%. The alkaline phosphatase was 40 King Angstrom units; the serum glutamic transaminase 70 units; the cephalin flocculation 0 units; the serum protein 3.5 grams% of albumin and 3.8 grams% of globulin. Upper gastrointestinal barium roentgeno-

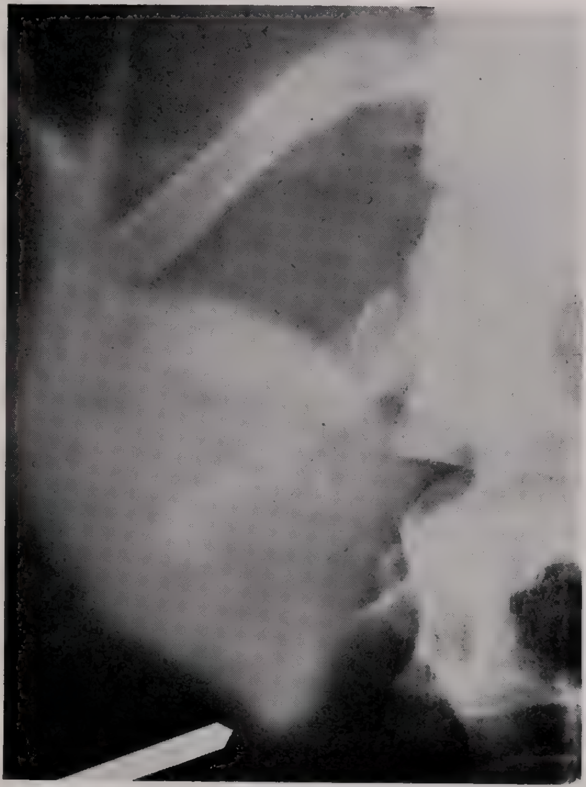

Fig. 2 — Intravenous cholangiogram of choledochal cyst. — Note the *pointed tip of the medial edge of the cyst.* Contrast increased by artist's retouching.

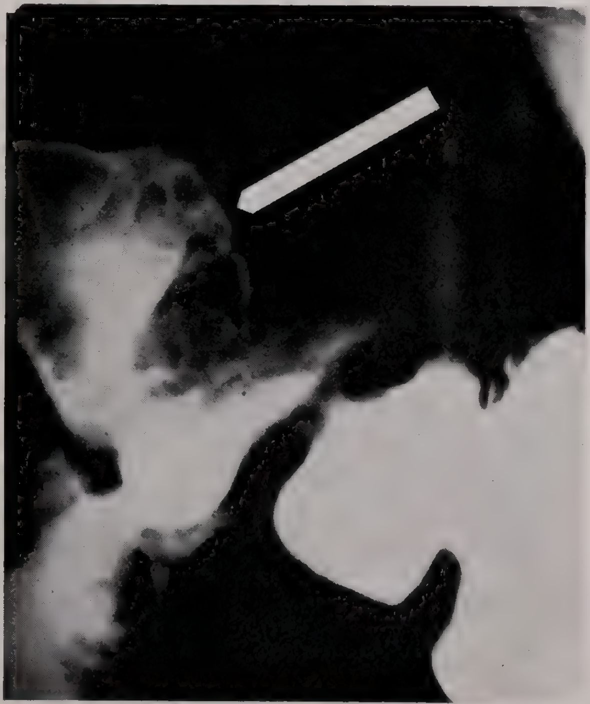

Fig. 3 — Postoperative upper gastrointestinal barium roentgenogram illustrating patency of the choledocho cysto-duodenal anastomosis. Arrow points to cyst.

grams showed duodenal compression to the left.

A preoperative diagnosis of choledochal cyst was made. Through a right subcostal incision a 10 x 8 x 6 cm. cyst containing 700 cc. of green bile was noted adjacent to the right side of the duodenum (Figure 1). A choledochocysto-duodenostomy was done. Radiography on the second postoperative day showed gas in the cyst. The patient was discharged on the eighteenth postoperative day, having had an uneventful recovery. Fifteen months later she was still free of symptoms.

Case 2

This 34-year-old negro mother gave a two-month history of chills, fever, jaundice, light stools and dark urine. Intermittent right upper quadrant abdominal colic had been present for six months, associated with vomiting and a 25-pound weight loss.

The physical examination showed icteric sclerae and right costal-vertebral tenderness, but no abdominal mass or tenderness. The stools were clay-colored.

The hematocrit was 46%; leukocyte count 4100; bile in the urine; direct serum bilirubin 9.5 mgm.%, with a total of 12.5 mgm.%; alkaline phosphatase of 22 King Angstrom units; cephalin flocculation 3+; serum protein 4.8 grams of albumin and 4.4 grams of globulin; serum glutamic oxy-transaminase 188 units; and a prothrombin time of 60%. Percutaneous needle liver biopsy showed biliary obstruction.

A choledocho-cysto-duodenostomy and a cholecystectomy were done for the 5-cm. retroduodenal choledochal cyst. In the immediate postoperative period bleeding from an aberrant artery caused shock requiring re-operation and ligation of the artery. The remainder of the postoperative convalescence was uneventful. An upper gastrointestinal roentgenogram five months later showed filling of the choledochal cyst.

Case 3

A 30-year-old white mother had post-prandial epigastric distress of four years duration. She had some fatty food dyscrasia and gas, but no nausea, vomiting, weight loss, jaundice, or abnormally colored stools or urine. A cholecystectomy had been done 18 months previously because of nonvisualization of the gallbladder by orally administered dye. No stones were found, but the common duct was reported to measure 3 cm. in diameter.

Physical examination showed a thin, white female with right upper quadrant tenderness. There was no icterus. Laboratory determinations were normal and of no diagnostic significance. Barium roentgenogram of the stomach and duodenum was also normal. Intravenous cholangiogram showed a slightly dilated common duct and a 3 x 8 cm. large sac with a *pointed tip* on the medial edge suggesting a choledochal cyst rather than a gallbladder (Figure 2).

A choledochocysto-duodenostomy was performed. The pointed medial tip of the cyst was found to be one cm. from the ampulla of Vater and a two-mm. probe could not be passed from the cyst through the sphincter of Oddi.

The postoperative course was uneventful. An upper gastrointestinal barium roentgenogram six weeks postoperatively showed barium reflux into the cyst (Figure 3). The patient has been free of symptoms except for occasional right upper quadrant abdominal pain following the eating of peanuts or coarse foods. Recently the patient had a normal pregnancy and delivery.

Comments and Conclusions

Cystic dilatation of the common duct, though rare, may be encountered by anyone performing biliary surgery. Perhaps one should routinely obtain an intravenous cholangiogram whenever a cholecystogram shows nonvisualization.

The classic triad of intermittent jaundice, abdominal pain, and a mass suggesting choledochal cyst is not uniformly evident.

Because of the relatively low operative mortality, choledochocysto-duodenostomy seems to be the treatment of choice.

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Papyrus Ebers[*]

To Extract Slivers

In the minor triad — bites, burns, and slivers, slivers were by no means ignored or neglected in ancient Egyptian therapeutics. The Ebers Papyrus lists a variety of salves for extracting splinters from tender flesh.

What to do to Draw Out Splinters in the Flesh

The per-baibait-bird-with-Honey
Apply thereto.

Another

Worms' blood, cook and crush in Oil;
Mole, kill, cook, and drain in Oil;
Ass's dung, mix in Fresh Milk
Apply to the opening.

Another

Skull-of-the-Shadfish, cooked in Oil
Apply to the point of the splinter. Thereby it comes out.

Another

Incense
Dough
Sea-salt
Wasp's dung
Fat

Another

Red-lead
Wax
Apply thereto. It draws the matter out.[**]

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[*] See Minnesota Med 48:1468, 1576 and 1694, 1965, and 49:124, 49:356, 1966.
[**] Bryan, Cyril: The Papyrus Ebers, D. Appleton and Company, New York, 1931, pp. 73-74.

God

I could prove God statistically. Take the human body alone — the chance that all the functions of the individual would just happen is a statistical monstrosity.

— George Gallup

Wherever you vacation this year, so many people will be there that you'll be lucky to know half the faces in your snapshots. — Changing Times

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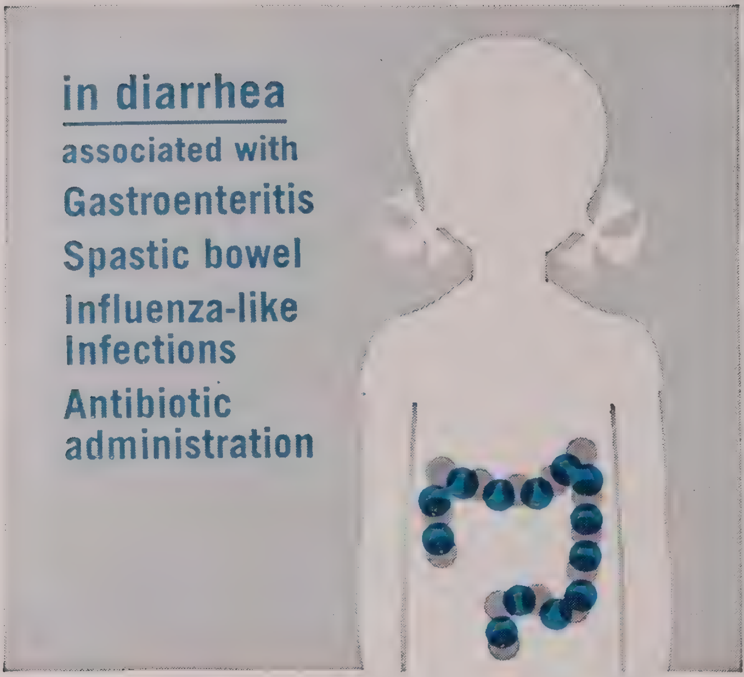
Someone has said that in this world a man must be either an anvil or a hammer. But he was wrong. Some men are neither — they are merely bellows.

— Arkansas Baptist

Life cannot go on without much forgetting. — Balzac


in diarrhea
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normal activity...

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atropine sulfate	0.025 mg.

Dosage: For full therapeutic effect—Rx full therapeutic dosage. The recommended initial *daily dosages*, given in divided doses, until diarrhea is controlled, are:

Children:

3 to 6 months	3 mg.	(½ tsp* t.i.d.)
6 to 12 months	4 mg.	(½ tsp. q.i.d.)
1 to 2 years	5 mg.	(½ tsp. 5 times daily)
2 to 5 years	6 mg.	(1 tsp. t.i.d.)
5 to 8 years	8 mg.	(1 tsp. q.i.d.)
8 to 12 years	10 mg.	(1 tsp. 5 times daily)

Adults: 20 mg. (2 tsp. 5 times daily or 2 tablets 4 times daily)

*Based on 4 cc. per teaspoonful.

Maintenance dosage may be as low as one fourth the therapeutic dose.

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Side Effects: Side effects are relatively uncommon but among those reported are gastrointestinal irritation, sedation, dizziness, cutaneous manifestations, restlessness and insomnia.

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SEARLE

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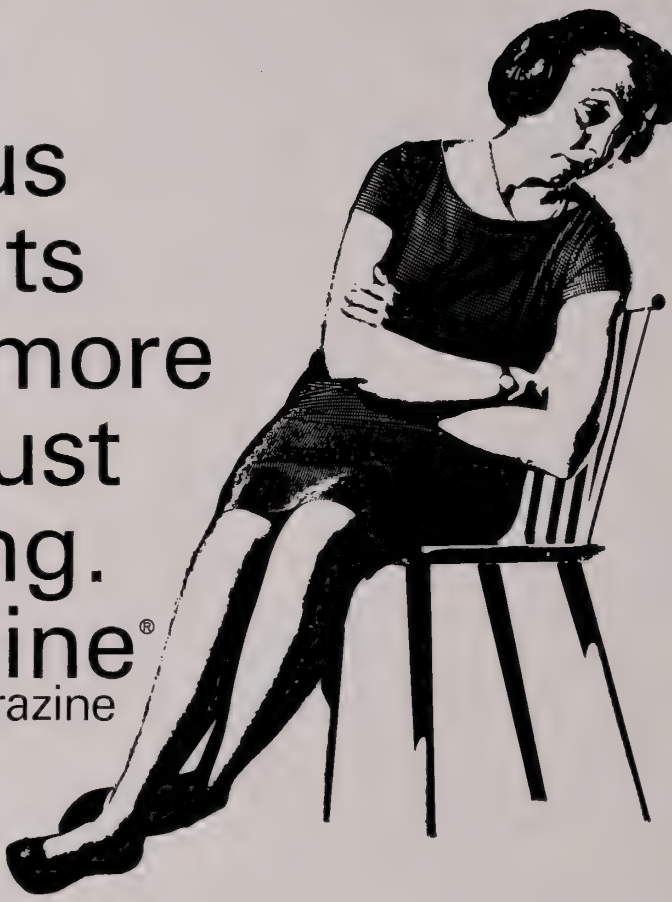

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Editorials

Hostility

SOME PHYSICIANS would like to concentrate their practice upon patients suffering from organic disease. They have been taught that a given constellation of symptoms and signs, plus corroborative laboratory studies, lead to a given disease which, when defined, can then be treated. What is not so carefully expounded is the fact that the identical symptoms and many of the other findings may stem not from the suffering organ but from the suffering ego. Some decry the neurotic patient as a nuisance cluttering up the office and unnecessarily filling the hospital beds. He is rejected by "You're not sick—it's all in your head" or repudiated by other means.

The patient whose nausea and vomiting are due to anorexia nervosa can vomit just as much and as hard as the intestinally obstructed patient. The sufferer from cardiac neurosis can be as equally incapacitated as the victim of valvular disease.

Therapy of such a patient is difficult and time-consuming, and the results are painfully slow. But success with these nervous individuals can mean many years of life—neurotic life to be sure; but this is beyond our purview.

Alan Challman in his article, "Hostility and Disease" in this issue,* discusses several facets of the problems the physician encounters with emotionally disturbed people. He examines in detail the factor of hostility that plays such a dominant role in human relations and is such a major impediment to the intimate patient-doctor relationship. Challman points out that not all the hostility comes from the patient; the physician too may be acting out (in a carefully camouflaged way of course) what amounts to hostility. It behooves the physician to study this fact of human behavior, especially to recognize and control his own hostility. The doctor who despises the neurotic patient may be reacting to his own inability to handle such a problem. He may envy the mechanic leaning over the knocking automobile engine who can say "The number 4 rodbearing is shot"; who can replace that part, and so stop the engine from knocking. It is because of the neurotic patients, the unpredictable humans who are the doctors' patients, that physicians are not mere mechanics. The key to many medical problems lies in recognizing emotional factors, existing in the physician as well as in the patient.

Reuben Berman, M.D.
Minneapolis, Minnesota

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*See page 523.

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Acute Calculous Cholecystitis*

IT IS indeed unusual to find Staphylococcus aureus as the cause of acute calculous cholecystitis. The uncomplicated postoperative course of the patient speaks well for the therapy that was instituted, since one might ordinarily anticipate that such an organism would cause great difficulty in the subhepatic space and in the abdominal wound.

It would be of interest to know if the culture showed massive growth of coagulase-positive Staph. aureus; if not, what was the number of colonies in the culture? Was there any evidence of obstruction in the duodenum which might account for the reflux up the common duct? Lastly, it would be quite interesting to know if the histologic sections showed organisms in the wall of the gallbladder or whether they were mainly cultured from the bile and from the purulent material contained by the gallbladder? It would perhaps be important to know also if the organism could be cultured from the bile from the common duct and biliary tree.**

This has, indeed, been an interesting finding and it is important that it has been brought to our attention.

William H. ReMine, M.D.
Rochester, Minnesota

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*See page 409.
**See page 458.

Cerebral Vasospasm

SPASM OF THE cerebral arteries has been the subject of much debate in the study of cerebrovascular accidents or strokes. It has generally been diagnosed when abrupt focal symptoms have spontaneously recovered without residual findings. It has been argued that such reversible injury to the cerebral tissue could not be caused by complete occlusion of an artery since recovery could not occur. The area would be devoid of arterial supply and in turn be severely injured and infarcted. Arteriospasm also has been alleged to persist long enough to result in permanent encephalomalacia.

For a long period, many neurologists and neuropathologists completely rejected arteriospasm as a cause of any form of stroke or cerebral injury. The transitory focal attacks were regarded as the secondary effect on the area surrounding small infarcts or hemorrhages. The neighboring regions were said to be involved by diachesis (shock) or edema, both of which are reversible. As long as the small central lesion involved only a silent area and the symptoms were secondary to the reversible neighborhood effects, recovery would be logical.

The excellent article on this subject in the January* issue of MINNESOTA MEDICINE brings out the important role cerebral angiography has played in our understanding of cerebral circulatory disease. Cerebral angiograms have demonstrated how small recurring focal cerebral episodes may result from stenosed or permanently occluded large cerebral arteries, either intracranial or cervical. The clinical picture is identical to that formerly ascribed to vasospasm. The surgical correction of the stenosed or occluded extracranial artery (carotid or vertebral) has led to recovery. This indicates an arterial insufficiency either of the main arterial supply or of the collateral circulation to the involved area. Such an insufficiency may result from any slowing of the cerebral circulation. This may be caused by an transitory drop in blood pressure. The desire to treat hypertension with too much vigor is a very common occurrence. In older people who are apt to be candidates for strokes, a mild hypertension might be superior to a normotensive state.

Continued

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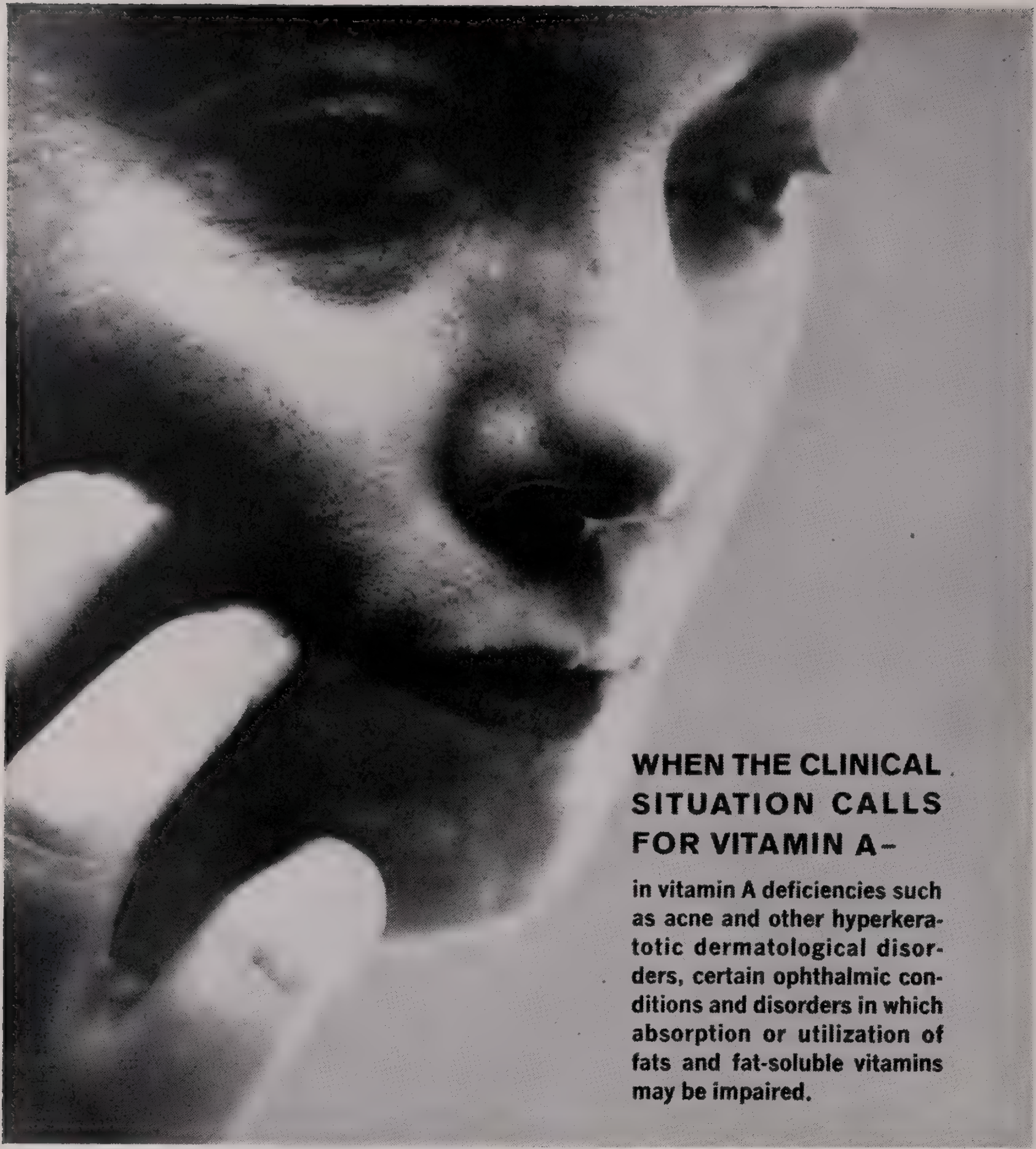
*See Minnesota Med 49:55, 1966.



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Brief mention should be made of the frequency of cerebral thrombosis. Over many years of examining brains in the neuropathological laboratory, the author has been impressed by the observation that a narrowed arterial lumen is more common than a thrombosis in the artery supplying the area of cerebral infarction. Perhaps in some cases the thrombosis had broken up or was dissolved by thrombolysin. These pathological observations along with angiography suggest that many cases of so-called cerebral thrombosis are actually cerebrovascular insufficiency. One case of massive encephalomalacia occurring one week after carotid artery surgery failed to reveal any vascular obstruction from the aortic arch to the brain. The site of the endarterectomy was normal. The patient was symptom-free and ready to leave the hospital. It seemed as if either transitory clotting or arterial spasm had occurred.

Strong evidence favoring arterial spasm as a cause of cerebral symptoms is seen in malignant hypertension and eclampsia. Segmental spasm of the retinal arteries of a temporary nature are seen. The article in this journal mentions the angiographic evidence for spasm in subarachnoid hemorrhage. Areas of infarction far from the site of the aneurysm appear to be caused by such spasm. The author has examined a brain showing diffuse cerebral atrophy and ventricular enlargement following repeated subarachnoid hemorrhages. Vasospasm was strongly suggested by the failure to find any pathological cause of the cerebral damage other than cerebral aneurysm. Also, a very thin layer of subarachnoid bleeding may lead to deepening coma and death. This is hard to reconcile with the mild degree of bleeding unless vasospasm is invoked. A case of pheochromocytoma* was published demonstrating segmental spasms producing a beaded appearance of the anterior and middle cerebral arteries that disappeared after removal of the adrenal tumor. I have observed one case with the same angiographic segmental appearance in the anterior cerebral artery. Following removal of the pheochromocytoma, the neurological symptoms and findings rapidly regressed.

There remains little doubt that spasms of the cerebral arteries occur and are important in certain cases and conditions. It seems likely that spasm may be associated with arteriosclerotic and occlusive vascular lesions in cerebrovascular accidents and intracerebral hemorrhages. The lesson learned from subarachnoid bleeding suggests that the degree of associated arterial spasm may be of great significance in certain cases. Even though great progress has been made, it is obvious that much research remains to be done in this field.

Harold H. Noran, M.D., Ph.D.
Minneapolis, Minnesota

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*See Test Your Word Score Page 447.

Mechanism and Management of Intravascular Thrombosis

THE EXISTENCE of multiple recognized forms of treatment for a clinical disease entity suggests either that there are multiple etiologies of the entity including some not yet recognized or that none of the treatment forms alone are adequate.

Thrombotic disease comes as close as any to fitting this category of diseases. An objective appraisal of the situation as put forth in the February issue by Spittell, Thompson and Owen* should be read by all physicians attempting to treat thrombotic disease states and noted especially by those adherents of the "one-treatment" technique of the surgical, drug or enzyme approach.

The surgical approaches of venous thrombectomy and ligation still have a limited application and should be resorted to infrequently. On the other hand arterial embolectomy and thrombectomy with endarterectomy are often the procedures of choice in certain arterial thrombotic disease cases.

The value of oral enzymes still so often used is to be questioned seriously. Blood levels of the enzymes in question have not been documented after ingestion of such medications. The results of this form of

Continued

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*See Minnesota Med 49:331, 1966.

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Contraindications: Previous allergic or idiosyncratic reactions to meprobamate or meprobamate-containing drugs.

Precautions: Careful supervision of dose and amounts prescribed is advised. Consider possibility of dependence, particularly in patients with history of drug or alcohol addiction; withdraw gradually after use for weeks or months at excessive dosage. Abrupt withdrawal may precipitate recurrence of preexisting symptoms, or withdrawal reactions including, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, the dose should be reduced and operation of motor vehicles or machinery or other activity requiring alertness should be avoided if these symptoms are present. Effects of excessive alcohol may possibly be increased by meprobamate. Grand mal seizures may be precipitated in persons suffering from both grand and petit mal. Prescribe cautiously and in small quantities to patients with suicidal tendencies.

Side effects: Drowsiness may occur and, rarely, ataxia, usually controlled by decreasing the dose. Allergic or idiosyncratic reactions are rare, generally developing after one to four doses. Mild reactions are characterized by an urticarial or erythematous, maculopapular rash. Acute nonthrombocytopenic purpura with peripheral edema and fever, transient leukopenia, and a single case of fatal bullous dermatitis after administration of meprobamate and prednisolone have been reported. More severe and very rare cases of hypersensitivity may produce fever, chills, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, anaphylaxis, stomatitis and proctitis. Treatment should be symptomatic in such cases, and the drug should not be reinstituted. Isolated cases of agranulocytosis, thrombocytopenic purpura, and a single fatal instance of aplastic anemia have been reported, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity has been reported, usually after excessive meprobamate dosage. Suicidal attempts may produce lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

Usual adult dosage: One or two 400 mg. tablets three times daily. Doses above 2400 mg. daily are not recommended.

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treatment do not stand critical analysis when compared with those observed after other better-documented methods.

Low molecular weight dextran and lytic enzymes, while offering a hopeful future, are still experimental methods and require further evaluation before their general use can be justified.

Numerous clinical and laboratory studies of the past two decades leave little doubt of the role of tobacco smoking in the etiology or aggravation of both venous and arterial thrombosis. Abstinence from smoking should be considered a must in the treatment of all thrombotic disease conditions.

It is worth remembering that bed rest with elevation of the foot of the bed in most cases of suspected or proven deep venous thrombosis of the lower extremities is still an effective form of treatment even without the use of anticoagulants. Immobilization is conducive to stasis and progression of the thrombosis, whereas muscular activity in bed or out increases venous flow and enhances clot dissolution. For this reason, whenever possible, patients who are put at bed rest for treatment of venous thrombotic conditions should be encouraged to move about in bed as much as possible. Immobilizing hot packs and tight bed covers should be avoided if possible. The hot packs certainly provide patent comfort and aid in the early resolution of the inflammatory process. As soon as the patient is comfortable, however, such packs should be discontinued.

Superficial venous thrombosis of the extremities, except when local discomfort precludes it, is resolved more rapidly by active ambulation with elastic support than by bed rest. Prolonged sitting or standing is to be avoided. In these cases there is little or no evidence that antibiotics or anticoagulants are of benefit. Observing the precautions of determining and monitoring the white blood count at weekly intervals during treatment, resistant cases of superficial thrombophlebitis often respond to anti-inflammatory drugs such as the phenylbutazone derivatives or steroids.

At the present time, as is brought out by Spittell, Thompson and Owen, heparin is our most perfect anticoagulant and should be used acutely in conjunction with the longer acting coumadin and indanedione derivatives for long-range treatment.

Davitt A. Felder, M.D.
St. Paul, Minnesota

Hyperventilation*

Spontaneous hyperventilation is a common clinical syndrome usually on an anxiety basis. It may present in pure form or as part of a more complex psychiatric syndrome such as hysteria or depression with anxiety features. Symptoms of hyperventilation, per se, may then be interspersed with other physical symptoms due to hysteria or the many somatic complaints which frequently are associated with depression.

The syndrome of hyperventilation may occur during the day or may awaken the patient at night. The common symptoms consists of numbness and tingling of the extremities, more in the hands, often with similar symptoms affecting the tongue and mouth. This is often followed by a feeling of lightheadedness and impending syncope, with stiffness of the affected parts of the body noted above. The main complaints are usually sensory and patients may neglect to mention breathing difficulty at the onset since they may be unaware of the disturbance in breathing pattern or because the sensory symptoms are so much more striking. Other patients will volunteer that the episodes began with a choking episode of respiratory distress, usually painless; or further inquiry may elicit this information. With the choking sensation, these patients may experience

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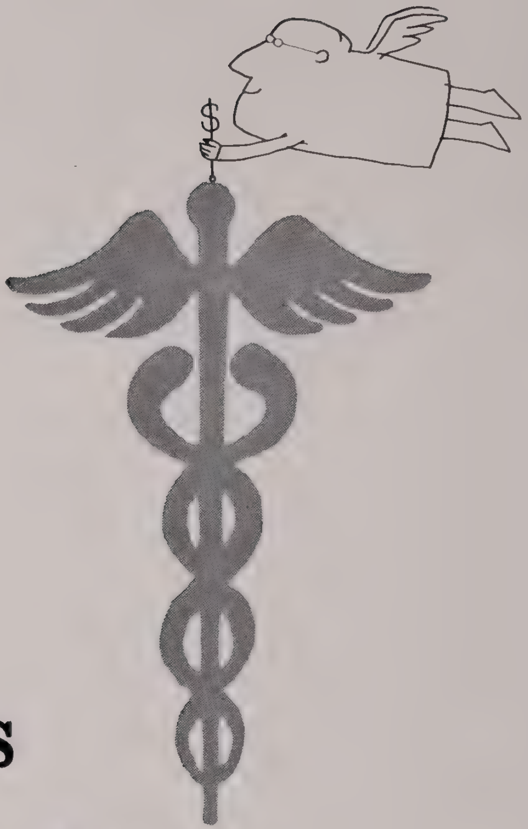
*Moriarty, James: Hyperventilation, Minnesota Med 49:159, 1966.



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a full feeling in the throat, a form of globus hystericus. Most of the episodes tend to relent with a calm, reassuring attitude on the part of the physician and proper use of sedatives, more to quiet the resultant symptoms of anxiety and to therefore reduce the tendency to recurrence.

Because of the occurrence of throat and breathing symptoms at the onset of an attack, one must consider the possibility of tracheal or esophageal difficulty as well as chest problems such as asthma, spontaneous pneumothorax, foreign body of the trachea or esophagus, diverticulum of the esophagus or retropharyngeal abscess. The sensory symptoms suggest the possibility of tetany associated with hypocalcemia, peripheral neuropathy, Guillain-Barre* syndrome (particularly with facial involvement), polyneuritis secondary to infectious or toxic involvements of the nervous system. With the episodic nature of hyperventilation, convulsive disorder must be considered.

Voluntary hyperventilation is a standard method of activation of the electroencephalogram. In normal adult tracings the pattern is not significantly changed by three minutes of hyperventilation even though the patient may experience mild symptoms of numbness and tingling of the extremities, tongue, and mouth. Slowing is almost always seen below the age of 14 or 15 with hyperventilation, and is quite frequent between the ages of 15 to 20. After the age of 20, slowing is almost always considered to represent an abnormal response, while prior to the age of 20, the nature of the response, such as paroxysms or focal disturbances, may be of significance. It is of interest that a true petit-mal pattern is precipitated in the EEG tracing by hyperventilation and, in fact, hyperventilation in the office will usually demonstrate a clinical attack of true petit mal. It is felt that EEG slowing due to hyperventilation is a manifestation of cerebral vasoconstriction; yet it is difficult to understand why it is so unusual after the age of 20 in normal patients, when pathological studies show that beginning cerebral arteriosclerotic blood vessel changes generally occur at age 30.

When a patient with hyperventilation syndrome is examined, the increased rate and depth of respiration may or may not be apparent. Sedation is frequently effective, but the underlying pathology may not be a pure anxiety, and therefore other measures must be considered, such as psychotherapy or the concomitant use of antidepressants in depression with depression and anxiety.

Harold Berris, M.D.
Minneapolis, Minnesota

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*See Test Your Word Score Page 447.

In the Shadow of Isolation

OUT ON THE fringes of society exists an institution created by man from the fear of mental anguish to be suffered by others. Here is a place apart, designed to protect a patient from himself, society from the patient, and in the process, to minimize public scandal.

It is intended that these hospitals will offer protective custody, provide modern efficient treatment, serve to train future professional talent and undertake research on the vast problems surrounding mental illness. Yet there is the impression of a conflict of social purpose, containing one segment of society in the shadow of isolation. Real concern would require that these patients be given every care and attention necessary to assure their continuance in useful and contributing roles.

International data suggest that major mental disorders have relatively constant incidence. Careful cohort studies back to the turn of the century show that the percentage of recoveries is also essentially constant, the duration of illness shortened, to be sure. For more than fifty years then, we have faced the fact that the majority of patients recover from mental illness. Yet the discrimination against the mentally ill persists. If this is not so, just answer:

Where are most state hospitals located?

Continued

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What is their size and rated bed capacity?

Where are the needed and qualified personnel?

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What professional training and research goes on there?

Is there a university affiliation for teaching, training and research?

Is mental illness included in most health insurance plans?

The answers are all too clear; these facilities and patients have historically not really been part of the community. It remains then to return the problem to where it belongs — for a community problem is a community responsibility.

The establishment of facilities and the type of program should have clear goals and be based on definite needs. Unfortunately these decisions are not always reached on the basis of clearly established need, as determined by epidemiological findings. Other demands, local, personal or social, may intercede.

In many ways mental health and social problems are interrelated. Public support and professional participation could be the cornerstone to future success, a success which we know is possible and within reach. With new understanding, new purpose and community involvement, the shadows could lift. The strength of family, community, occupational and professional ties has a cohesive therapeutic and socializing effect and from this matrix could emerge a new era of community mental health, social responsibility and human welfare.

Herbert Dorken, Ph.D.*
Sacramento, California

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*Former Director, Community Mental Health Services, St. Paul, Minnesota. Presently, Chief, Bureau of Psychology, Department of Mental Hygiene, Sacramento, California.

Test Your Word Score

Cerclage — *an encircling suture, tightly drawn* (page 394).
Myocardosis — *symptomatic of cardiac disease without discoverable pathology* (page 403).
Extracorporeal circulation — *outside the body* (page 425).
Pheochromocytoma — *adrenal tumor secreting hormone* (page 441).
Guillain-Barre — *pronounced ge-yan' bar-a'* (page 445).
Antigenicity — *potency as an antigen* (page 479).
Endarterotomy — *removal of plaques of intima from a large artery* (page 504).
Epicardiectomy — *an operation by which the heart is supplied with a collateral circulation from the pericardium* (page 505).
Post-cibal — *after taking food* (page 509).
Explication — *elucidation, interpretation* (page 524).
Cardioversion — *coined: changing the heart rate by electrostimulation* (page 550).

Letter to the Editor:

I have noted your soliloquy on Medicare.* I am particularly sensitized to this problem, having spent over three years of my short medical life

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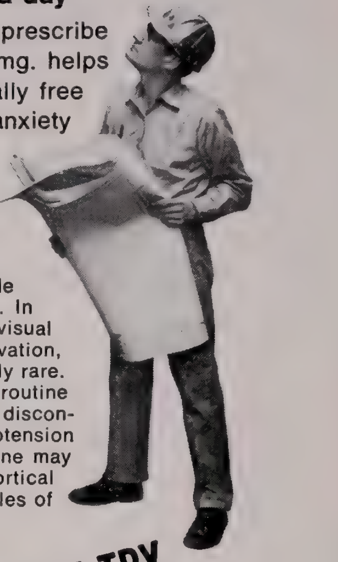
*See Minnesota Med 48:1169, 1965.

Continued



Blueprint for dealing with tension due to stress — Prolixin — once-a-day

For the patient who must be on the job mentally as well as physically, prescribe Prolixin. The prolonged tranquilizing action of as little as one or two mg. helps him cope with tension all day long. Markedly low in toxicity and virtually free from usual sedative effects, Prolixin is effective in controlling both anxiety associated with somatic disorders and anxiety due to environmental or emotional stress. Patient acceptance is good — because Prolixin is low in cost, low in dosage and low in sedative activity. Prescribe Prolixin.

Side Effects, Precautions, Contraindications: As used for anxiety and tension, side effects are unlikely. Reversible extrapyramidal reactions may develop occasionally. In higher doses for psychotic disorders, patients may experience excessive drowsiness, visual blurring, dizziness, insomnia (rare), allergic skin reactions, nausea, anorexia, salivation, edema, perspiration, dry mouth, polyuria, hypotension. Jaundice has been exceedingly rare. Photosensitivity has not been reported. Blood dyscrasias occur with phenothiazines; routine blood counts are recommended. If symptoms of upper respiratory infection occur, discontinue the drug and institute appropriate treatment. Do not use epinephrine for hypotension which may appear in patients on large doses undergoing surgery. Effects of atropine may be potentiated. Do not use with high doses of hypnotics or in patients with subcortical brain damage. Use cautiously in convulsive disorders. **Available:** 1 mg. tablets. Bottles of 50 and 500. For full information, see Product Brief.

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in western Europe where the practice of medicine has been taken over by the State. May we be saved from that total loss of individual initiative.

Arndt J. Duvall, III, M.D.
Minneapolis, Minnesota

The Editor's Soliloquy

The 'Gimmie' Syndrome

Until 1932 this indigenous syndrome was too rare to have been recognized and described, but since that year it has become so progressively and alarmingly evident as to be distinctly noticeable in the native population.

In those who develop this insidious malady the hands are often found to be extended in supine position as if for the receiving of gratuities; and there is a coarse, centripetally oscillating tremor of the palms suggestive of a mendicant's beckoning. Though the hands are soft, smooth, and free of tyloma, frequent calluses are observed over the olecranon and the ischial tubera.

The patient's skin is sallow — with a yellowish cast over the dorsal area of the back.

The muscles appear partially atrophied, unresponsive to stimulation or command, as the patient sits in apparent catatonia from morning until night anticipating personalized attention and favor.

Because of an excellent appetite these patients usually carry an excessive deposit of subcutaneous fat. Though the blood pressure, temperature, and respiration are normal, the pulse is torpid and the bowels are sluggish — often to the point of obstipation.

Ironically, fertility is unimpaired — or even augmented.

While the intellect seems normal, the personality has deteriorated: there is no ambition, no initiative, no desire for personal achievement and independence. Incentive and drive have vanished, and moral inanition has set in.

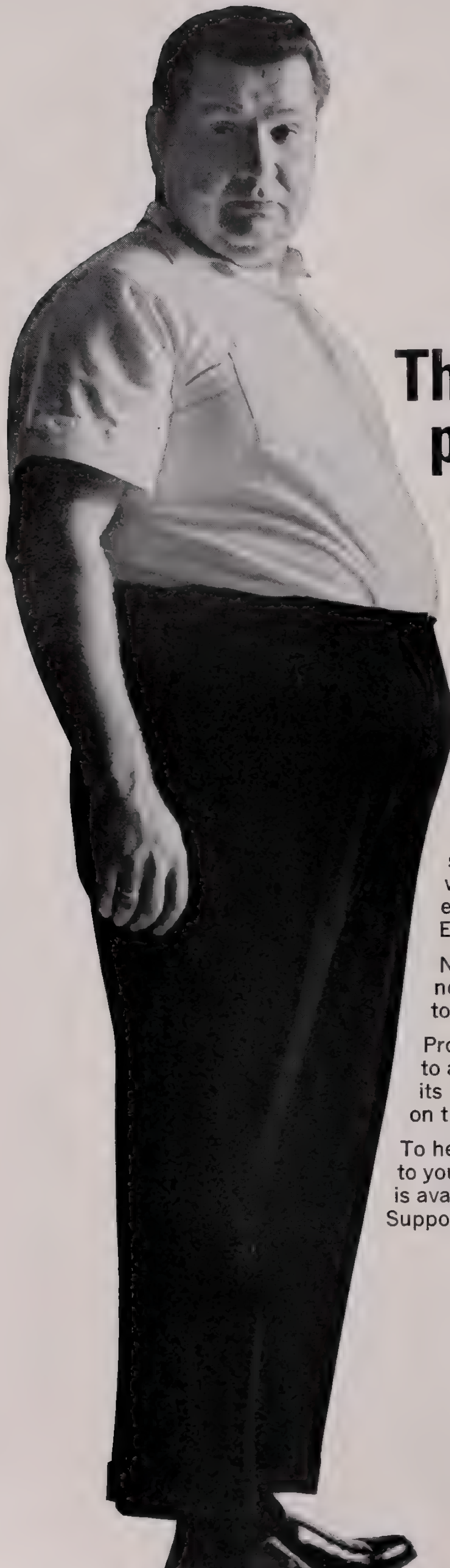
However, the apathy of these patients can be deceptive. At the slimmest prospect of extra handouts, further doles, increased compensation, or additional subsidies, a greedy glint can appear in eyes hitherto dull; necks previously inert can suddenly swivel to scan promising horizons; and lethargic bodies can galvanize into frenetic activity, utterly belying their former lassitude and immobility.

Like addicts, these sick individuals have an uncontrollable impulse to brazenly implore and shamelessly accept from society and government what they themselves would deny to others.

They have the 'gimmies.' — **Carl O. Rice, M.D.**

Mom says: If you can please a person you teach him much; if you disturb him you can teach him nothing.

Nothing has such power to broaden the mind as the ability to investigate systematically and truly all that comes under thy observation in life. — Marcus Aurelius



The population explosion

Chomp. Chomp. Chomp. He's off again on another spree of second helpings.

Tomorrow, crash! He'll be on a newfangled diet. Starving himself.

He's just one of the many who bounce between starvation and overeating, and with every rebound make losing weight more difficult.

As a professional, you can help. First by pointing out that skipping meals is no solution, and second by recommending long-range weight control through sensible eating habits and nourishing foods. Every day. Day after day.

Naturally, balanced diets and nourishing, palatable dairy foods go together; they always have.

Project Weight Watch has been initiated to assist you. Its scope is nationwide, its purpose is to focus professional attention on the problem.

To help you translate your concern to your patients, a portfolio of materials is available. Send for it. Support girth control.

Dairy Council of the Twin Cities
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Servicing the Greater Twin City Metropolitan Area

PROJECT
WEIGHT
WATCH

(Continued from page 391.)

disavowals of the exercise of supervision or control of Section 1801.

3. That maximum use of hospital staff authority, fiscal intermediary evaluation, and cooperative efforts should be relied upon for quality control of utilization reviews.

4. That state agency involvement in case review and survey or evaluation of active committee function be prohibited, or limited to assessment of the adequacy of 'Plans as submitted under proposed Standard Two.' "

Standard Two is the proposed outline of the structure and description of duties for utilization committees to follow.

During 1965 the American Medical Association published, circulated to all state association offices and made available to all interested physicians, hospital staffs and administrators a comprehensive handbook, "Utilization Review."

Basically designed for medical staff use, the handbook provides not only a guide to the establishment and functioning of a medical staff utilization committee, but explores the need, the philosophy, and the areas in which committees should function.

Aware of the established interests of consumers, third party payers, and government regulatory agencies in financing medical care, the handbook is built around recognition of the fact that "the medical profession should bear the majority responsibility for reviewing and policing utilization and quality controls."

The Minnesota State Medical Association remains active in utilization committee developments through attendance by the Chairman of the Committee on Medical Service, Dr. John Pewters, at the American Medical Association Medical Service Conference prior to the American Medical Association meeting, through the letter directed to presidents and secretaries of component medical societies by the Chairman of the Council, and through Council consideration and review of American Medical Association Technical Advisory Committee reports.

The situation is fluid, and changes are almost certain, through interpretation of the law, through developing regulations, and through vigorous, continuing presentation and defense of the unyielding opinion of physicians that regulatory mechanisms in medical care are medicine's responsibility, historically developed and imposed on physicians, by physicians, and always directed at improvement in patient care.

Utilization committees are now a requirement for participation in Medicare, but these actions by the Minnesota State Medical Association and the American Medical Association, prior to the passage of the Medicare Law, indicate the voluntary concern of every physician for every patient's welfare. That compulsion has now entered the picture does not modify that concern, nor should it be a source of physician alarm, as long as medicine continues to clearly identify that prior concern, as well as a continuing insistence on physician, not governmental, regulation of patient care, and of physicians' services.

RP Buckley M.D.

R. P. Buckley, M.D.
President
Minnesota State Medical Association

Food and Exercise

A man's food has much to do with the exercise of his gifts. It affects his ability to sing, to pray, to reason, to talk, to lead. A hearty meal of the plainest fare, or a very small quantity of richer food, will often clothe my soul with torpor, make my brain feel like a log of wood, and render speaking or writing a positive torture. — General Booth of the Salvation Army.

You prescribe elastic stockings.
She won't wear them.
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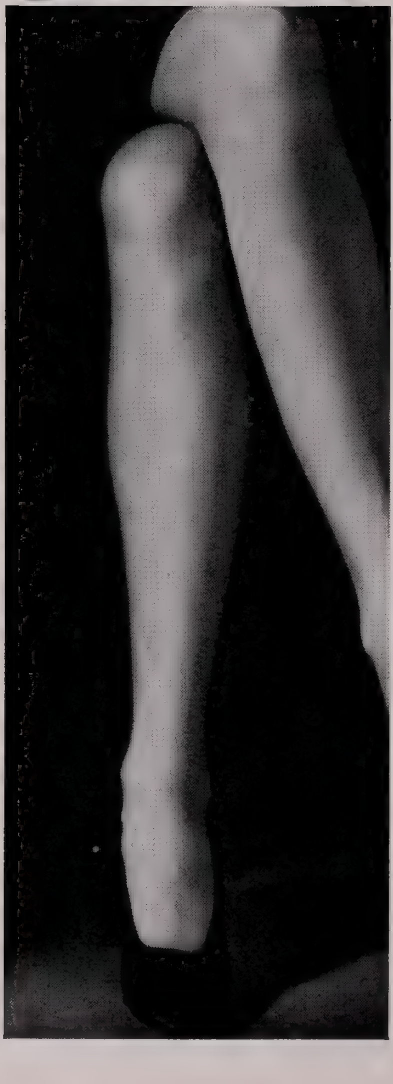

Elastic Stockings so sheer they look like support hose. Both Ultreer and support hose are sheer, shapely, cool and comfortable. But that's where the similarities end. New Ultreer fits firmly and evenly over the entire leg. Gives true therapeutic compression necessary to relieve varicose veins and other leg disorders. They provide the therapy you prescribe. The fashion and economy she demands. Ultreer stockings have a new low price. So low, she can afford two pairs of Ultreer instead of one pair of regular elastic stockings. There'll be no disagreements there. Ultreer stockings are as comforting to her purse as they are to her legs. New Ultreer are the elastic stockings doctors and women can agree on.

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Curbstone Consultation

Trichomoniasis

QUESTION: What has been the most valuable therapeutic management of trichomoniasis?

ANSWER: There is no question that vaginal trichomoniasis is excellently treated today by metronidozole (Flagyl). This is the first and only specific agent that has been developed. It has stood critical appraisal by a number of competent investigators. This therapy is one 250 mg. tablet three times daily for 10 days. These tablets should be taken with each of the three meals. The therapy is completed in 10 days. The husband should not be treated unless he is found to be infected and thus needs the therapy. In our experience an insignificant number of husbands were found to be contributing to the wife's infection. It is now the working rule that only the husbands of the women who have had over two outright failures by metronidozole are subjected to urological investigations. It is unwise to treat the husband without proper examination and diagnosis. He is treated only when an indication exists for it.

H. Close Hesseltine, M.D.
Dept. of Obstet. & Gynec.
University of Chicago

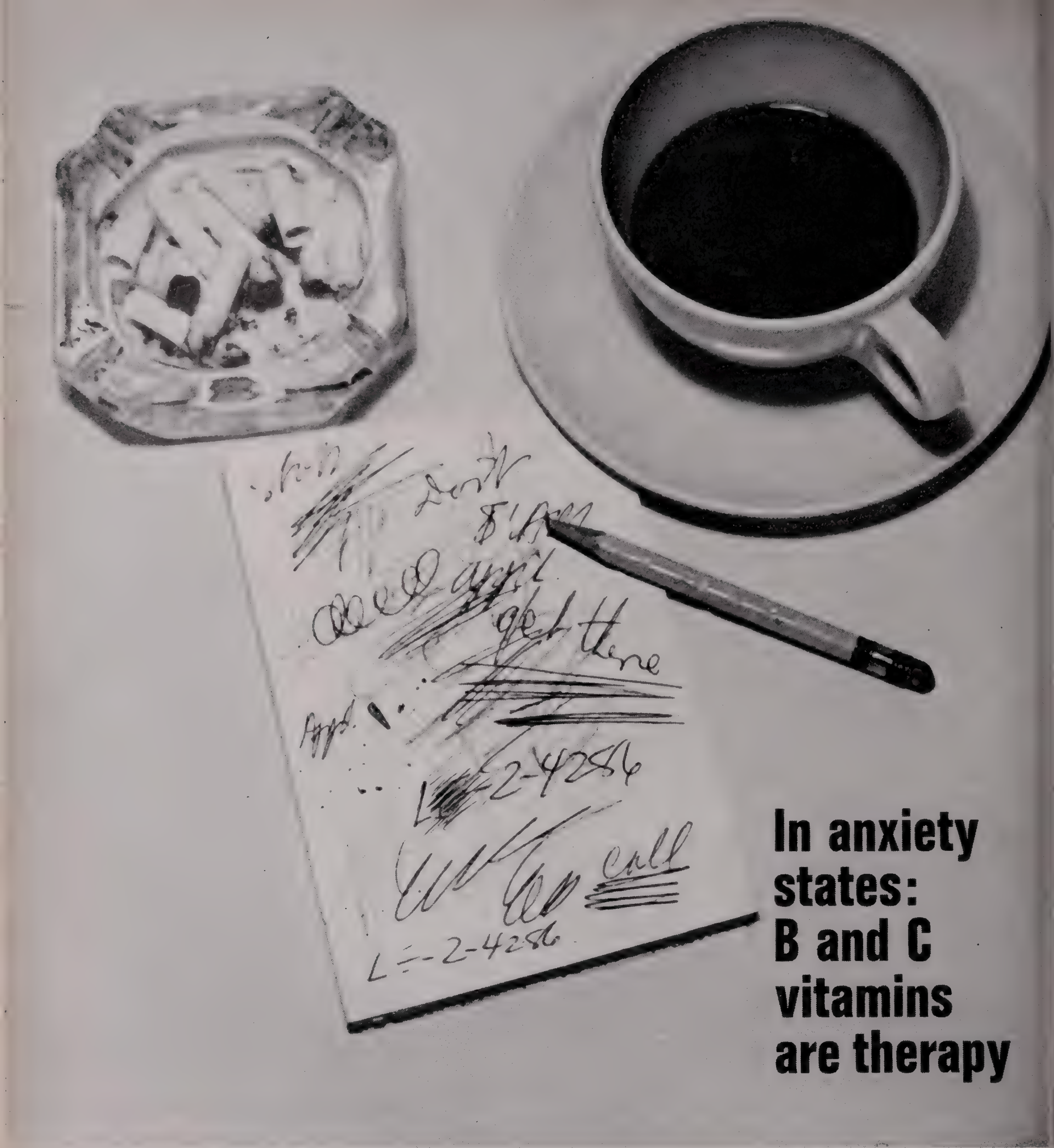
Enovid

QUESTION: What is the usual method of prescribing?

ANSWER: Most of our experience has centered around the use of Enovid. The drug is given in the same fashion as for ovulation control, starting on the fifth day of the cycle and being given for twenty days. In order to avoid nausea, the drug is usually given at night time. We try to give at least 0.1 mg. of mestranol. Therefore, with ordinary Enovid, if the patient tolerates the drug, we give 10 mg. per day. We have recently started using Enovid-E. It is possible that a single tablet will be effective here. Experimental data would also indicate that norinyl will be equally effective.

John S. Strauss, M.D.
Associate Professor
Boston University
Boston, Mass.

There is more power in the open hand than in the clenched fist.
— Herbert N. Casson



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Each capsule contains:

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Vitamin B_2 (Riboflavin)	10 mg.
Niacinamide	100 mg.
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Vitamin B_6 (Pyridoxine HCl)	2 mg.
Vitamin B_{12} Crystalline	4 mcgm.
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Recommended intake: Adults, 1 capsule daily, for the treatment of vitamin deficiencies. Supplied in decorative "reminder" jars of 30 and 100; bottles of 500.

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The Viewing Box

Systemic Scleroderma

This thirty-nine-year-old attractive Indian lady was admitted for the investigation of a dysphagia that had been progressive for several months. She complained that "solid food seemed to stick in the throat." Yet too much liquid caused her to bloat and develop a mild, crampy abdominal pain. She had been hospitalized for several days three months previously with a suspected intestinal obstruction which promptly subsided on medical management. For six months she had had a polyarthralgia, suspected of being rheumatoid arthritis. The sedimentation rate was 109. Recently she had begun to develop tingling in her fingers and toes, which often became bluish when exposed to cold. There was also some limitation of motion of the hands.

From this rather characteristic history you may already suspect the diagnosis. However, on the above G.I. series and small-bowel follow-through there are three gross roentgenographic findings which are so specific as to enable the perceptive observer to make the correct diagnosis without history (Figures 1, 2, 3). The history, however, does tell you where to look. Can you spot the significant X-ray features and give the answer?

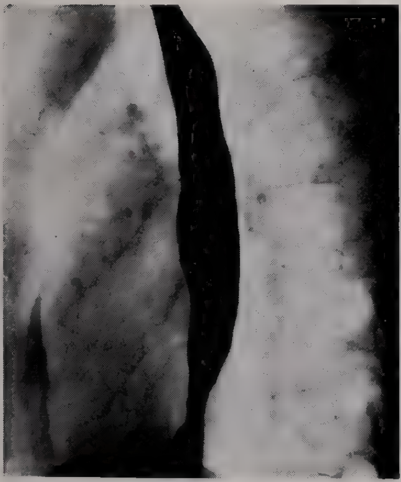

Figure 1

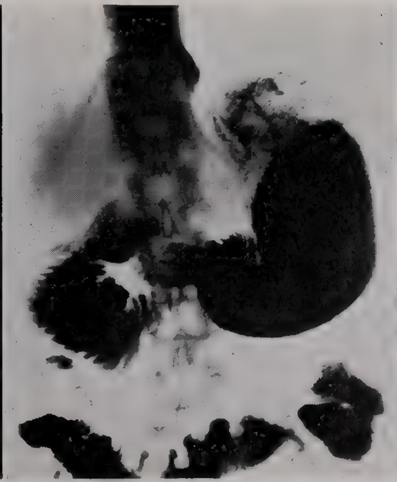

Figure 2

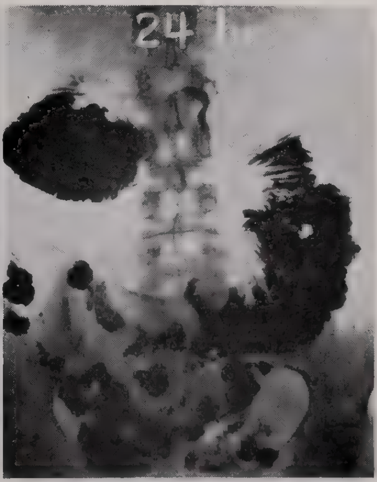

Figure 3

Continued

Editor's Note: X rays reproduced in the positive instead of the negative. Future X rays will appear in the negative.

Diagnosis: Systemic scleroderma.

The correlated roentgenographic findings here which are specific for this diagnosis are: (1) smooth constriction of the lower esophagus three or four centimeters above the diaphragm (Figures 1, 2); (2) dilated duodenal bulb and loop retaining barium for 24 hours (in spite of usual ambulant hospital activity) (Figures 2, 3); and (3) a sharp cutoff just beyond the flexure of the duodenum extending obliquely downward and slightly laterally (Figures 2, 3). This last finding is thought to be due to a pressure effect of the superior mesenteric artery on the stiffened and thickened wall of the duodenum.[5,8] Other nonspecific roentgenographic abnormalities are present in the jejunum and ileum (Figures 2, 3).

Tuffanelli and Winkelman,[11] in a study of 727 cases from the Mayo Clinic, reported that the diagnosis is about all the physician has to offer in this condition; "the etiology remains obscure; the course is unpredictable and the therapy is of little benefit." This is not a rare disease, however, as manifested by the fact that an average of 41 new patients with systemic scleroderma are seen each year at the Mayo Clinic.

The above patient had the acrosclerotic form of the disease, which is by far the commoner of the two types of systemic scleroderma. The skin changes were not striking when the diagnosis was first made. Her initial symptom was arthralgia, as was the case in 12% of the Mayo Clinic series.[11] Early in the course of the disease this symptom is often misdiagnosed as rheumatoid arthritis. The Raynaud's phenomenon and acral cutaneous sclerosis (below the mid-forearm) appear later and in that order. The acrosclerotic type favors the female over the male in a ratio of three to one. The age predilection is 20 to 50. The pathologic process frequently involves the gastrointestinal tract and other systemic organs, esophageal involvement being by far the most frequent type of gastrointestinal involvement.[4,11] Small bowel changes occur in as many as 12% of the cases of Reinhardt and Barry[8] and may be either specific or nonspecific. Occasional patients, such as ours, have presented with a picture of intestinal obstruction,[2,8] and others with a sprue-like syndrome.[3] Stomach[10,11] and colon[6,11] changes rarely have been reported. Pulmonary involvement occurs in one fourth of the cases and consists of fibrosis and sometimes cystic changes, predominantly in the lower half of the lung fields. Not infrequently cor pulmonale develops. Cutaneous calcification occurs late, on an average of 11 years after the onset of the disease[7,11] and is most frequently seen in the hands. In general the course in the acrosclerotic type is chronic.

The diffuse type of systemic scleroderma occurred in only 5.4% of the series of Tuffanelli and Winkelman.[11] In this type there is usually a central generalized cutaneous sclerosis. The extremities are spared and Raynaud's phenomenon is absent. The course is rapid and the prognosis extremely poor. The systemic manifestations are the same as those mentioned in the acrosclerotic form. Radiologic examination of the esophagus, stomach and small bowel should be performed in all cases suspected of having systemic scleroderma. Changes are not infrequently present before gastrointestinal symptoms develop.[8]

H. C. Walker, Jr., M.D.*
Minneapolis, Minnesota

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*Departments of Radiology, V. A. Hospital and Hennepin County General Hospital.
References may be secured from the author or the reprint.

Fracture–Trauma Conference

The Elusive Malar Fracture

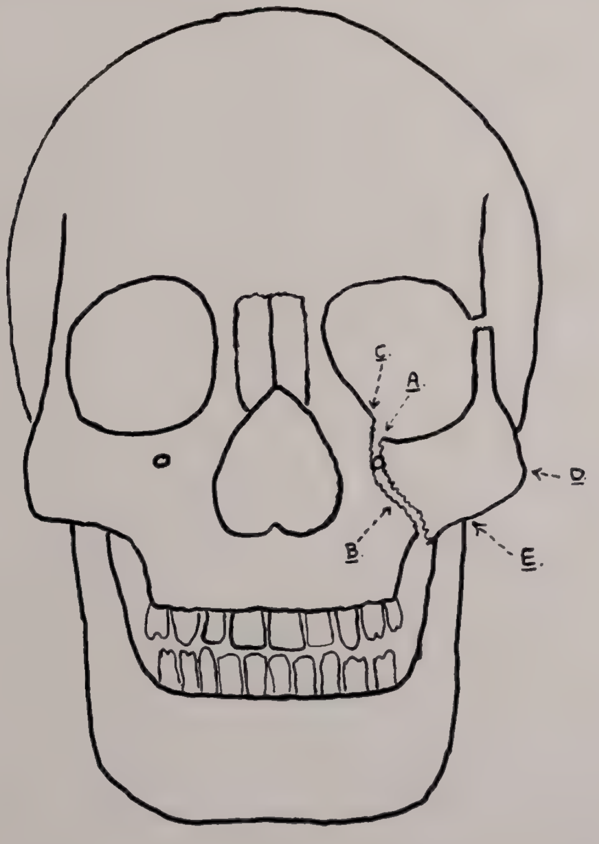
Clinical History — Accident, fell on cheek, blow over cheek

Clinical Examination — Usually considerable swelling and ecchymosis about cheeks and eyelids, "black eye." Swelling may obscure flatness of cheek prominence and notching of infraorbital ridge. Fractures may be difficult to visualize on "skull films."

Specific Inquiry to Suspect Zygoma Fracture

Fractures usually occur at thinnest and weakest portion of bone.

A. Numbness infraorbital nerve distribution — injury in fracture site.



Continued

B. Unilateral epistaxis — lateral antral wall involved.

C. Diplopia — may have "double vision" if inferior oblique or inferior rectus involved in fracture site.

D. Flatness over cheek prominence — due to inward depression of bone. Better appreciated by viewing cheeks tangentially from above forehead. Swelling over cheek often obscures flatness and delays complete appreciation of underlying depressed fracture.

E. Restriction of lower jaw motion. Inward depression of arch portion of zygoma reduces space between mandibular coronoid process and zygoma, producing a "tightness" or "binding" on lower jaw movement.

Roentgenographic Exam to Confirm Presence of Fracture

Water's view (chin on plate) best. Fracture line along infraorbital ridge. Clouding (blood) antrum on involved side. Body and arch depressed inward (may be best seen on vertico-submental view).

Operative Reduction of Depressed Zygoma Fracture

Outward and upward traction by grasping forceps inserted into bone through cheek skin.

Elevation of zygoma by instruments inserted under portions of bone.

Open surgical exposure of fracture sites with wiring may be required to maintain corrected position.

Early diagnosis helpful to allow operative reduction in first few days if possible. Reduction of bone to original position more difficult and less satisfactory as time elapses.

Lyle V. Kragh, M.D.
Minneapolis, Minnesota

(See Acute Calculous Cholecystitis, page 439.)

Did the culture show massive growth of coagulase positive Staph. aureus?

Yes, it did, and no other organism was grown.

Was there any evidence of duodenal obstruction?

No. Neither at surgery nor pre or post-operatively.

Did the histological sections of the gallbladder show organisms in the wall, was the culture mainly from the bile and purulent material in the gallbladder, was the organism cultured from the bile of the common duct and biliary tree?

The histological sections of the wall of the gallbladder showed multiple micro-abcesses scattered throughout which were packed with PMNs. Only the content of the gallbladder was cultured; the remainder of the biliary tree was not opened.

Robert P. Belin, M.D.
Minneapolis, Minnesota

Tumor Conference

Cystosarcoma Phyllodes

A 39-year-old married white female was admitted for an elective excision of a 3-cm. firm, nontender, somewhat lobular and nonfixed mass of the left breast of three months duration. Frozen section was suspicious of malignant cystosarcoma phyllodes, and paraffin sections were awaited before determination of definitive surgery. The tumor was considered malignant. Outside pathological consultation advised radical mastectomy because of the highly disturbing epithelial components. The radical breast operation was done; the specimen showed no residual tumor, and all of the lymph nodes were negative.

Without the disturbing histologic findings suggesting malignancy, a simple mastectomy would have been the operation of choice. The malignant changes in the epithelium are not sufficient to classify this case as a carcinoma. The combination of carcinoma and cystosarcoma phyllodes within the same tumor has been reported in only one case.[1]

Comments

Cystosarcoma phyllodes is an uncommon fibroepithelial tumor of the female breast. As the clinical behavior does not always follow the histological pattern,[2] Treves[3] aptly described this lesion as the Dr. Jekyl and Mr. Hyde of the breast. Over 43 different terms have been ascribed.[4] Much confusion has arisen in the literature in regard to the microscopic classification and related surgical treatment. This frustration is due in part to the inability of pathologists and surgeons to gain a wide clinical experience with this neoplasm. Furthermore, the term cystosarcoma phyllodes, originally applied by Johannes Mueller and Chelius[5] to a benign tumor, has remained as a descriptive term for a neoplasm which is either benign or malignant. Some authors,[6] however, state that this lesion is not malignant but simply a fibroadenoma with sarcoma-like stroma. A recent report by Oberman[7] has helped to clarify this subject. He would prefer to designate those neoplasms with benign stoma as "cellular adenofibroma" and those with malignant stroma as "periductal fibrosarcoma." Yet the term remains and thus the confusion continues.

According to Oberman,[7] it is now generally accepted that cystosarcoma phyllodes is a fibroepithelial tumor characterized by an increased cellularity of the mesenchymal stroma. This does not inclue mesenchymal lesions of the breast that have no epithelial component. It is unfortunate that the qualifying terms 'benign' and 'malignant' have been added; between these, Treves and Sunderland[8] have placed a "borderline" group in which the

Continued

pathologist cannot categorically state whether the tumors are microscopically benign or malignant.

The lesion may occur from adolescence[9] to old age, with the average age around 50. Bilateral occurrence is rare.[2,3,10] Grossly, the lesion may rapidly attain massive size and weigh several pounds,[5] but a small tumor does not rule out cystosarcoma phyllodes. In 93 cases reported by Treves,[3] 29 were 2 cm. or less and one case of 1 cm. size was malignant. Oberman[7] has also emphasized this feature. With rapid growth or massive size, skin ulceration and avascular necrosis may occur. Necrosis and ulceration do not signify malignancy but only loss of blood supply.[3] With malignant tumors, growth may extend into the pectoral muscles, ribs and pleura.[7,8] Metastasis is by the blood stream.[3,7,8] Lymph-node metastasis was reported in one case by Treves.[3] Cooper and Ackerman[11] also reported a case with lymph-node metastasis; however, no mention of an epithelial component within the breast tumor is made. When metastasis occurs, progression is usually rapid.[3] The metastatic lesions are composed of sarcomatous stroma with no epithelial component.[2,3,7,8]

Gross Appearance

Grossly,[2,4] the tumor is greyish white, fleshy and mucoid; it appears encapsulated, and its cut surface tends to "bulge" out. Cyst-like spaces may be present.[2,3,5] With large tumors, distended veins[3,4] are often seen covering the affected area of the breast.

Histologic Appearance

Microscopically, benign cystosarcoma phyllodes has hyperplastic stroma without atypism.[7] Hypercellularity may be more prominent near the epithelial elements.[7] The ducts may be elongated and compressed. Papillary infolding of the epithelium can occur along with intraductal epithelial proliferation. Orderly mitoses and multinucleated giant cells are common. Oberman[7] stresses this feature and emphasizes that such findings do not indicate malignancy; in nine benign cases,[7] orderly mitosis near the ducts was found. Zones of cartilaginous and osteoid metaplasia have been reported.[2]

Microscopically, malignant cystosarcoma has marked focal cellularity and severe nuclear atypism, with atypical mitotic activity.[7] This atypism and activity are removed from the periductal areas and may be found at the periphery of the tumor or in the adjacent fat.[7] The sarcomatous areas may be only focal in nature and consequently easily overlooked.[2,3,7,8] Thus, much emphasis has been directed to the absolute necessity of obtaining multiple samples before a lesion has been labelled benign. This feature, in the past, has led to inadequate surgical removal.

Between the benign and malignant group Treves[3] has placed a borderline classification in which there is a mild atypism of the stromal cells. Oberman[7] prefers the term low-grade malignancy.

The incidence of malignancy cannot be accurately assessed unless the authors have made adequate sampling of the tumor. Following this standard, Treves[3] has reported 15 malignant lesions in 93 cases (16.6%), Oberman[7] seven in 18 cases (38.9%), and Lester and Stout[2] 20 in 56 cases (34.4%). In spite of adequate sampling of the tumor, final analysis may not be possible unless the lesions have recurred with a histologically malignant picture or have metastasized.

Treatment

Surgical treatment[1,2,3,4,7,12] requires wide and complete removal of the neoplasm. In order to prevent local recurrence, benign lesions should be removed widely, not merely by biopsy excisions. Large benign neoplasms may thus require simple mastectomy. Malignant lesions are best treated by mastectomy with removal of the pectoral fascia and pectoral muscles if necessary.[7] Extension of the tumor may necessitate removal of a portion of the chest wall. Borderline or "low-grade" neoplasms should be treated by simple mastectomy unless a small lesion can be "widely" excised. Metastasis occurs via the blood stream and thus radical mastectomy is not deemed necessary.[7]

It is essential that a careful follow-up of these patients be made.

Deaths from cystosarcoma phyllodes are uncommon. Mortality rates in malignant cases cannot be accurately ascertained because of the confusion in reporting. Where careful studies have been reported, it would appear that an 18% figure would be close:

	Malignant Cases	Deaths	%
Treves[3]	15	1	
Lester & Stout[2]	21	3	
Oberman[7]	7	4	
	43	8	18.7

Summary

A case of malignant cystosarcoma is reported in which a radical mastectomy was performed because of the highly disturbing epithelial components.

Cystosarcoma phyllodes is an uncommon fibroepithelial tumor of the breast which requires thorough pathological sampling. Classification may be difficult. The clinical course does not always follow its histological appearance and thus careful follow-up of the patient is essential.

Regardless of the microscopic picture, wide excision should be done. Metastasis occurs via the blood stream, and in these cases progression is usually rapid.

Because Johannes Mueller used the term cystosarcoma phyllodes, its classification has since caused a great deal of confusion.

C. D. Adkins, M.D.
Minneapolis, Minnesota

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Science

Look at those cows and remember that the greatest scientists in the world have never discovered how to make grass into milk. — Michael Pupin

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Anorectal Surgery

Is Urinary Retention a Necessary Complication of Anorectal Surgery?

Urinary retention following surgical procedures on the anal canal and lower rectum occurs in thirty to forty percent of patients in most reported series. When urinary retention occurs, the bladder must be catheterized from one to three times, and in some patients it becomes necessary to insert a Foley type of indwelling catheter. Far too often the insertion of a bladder catheter is followed by urethritis and cystitis with the usual symptoms of frequency, burning, lower abdominal discomfort and fever. Chemotherapeutic and antibiotic treatments of urethral and bladder infections are expensive, not always efficacious, and at times lead to further complications.

The accepted cause of urinary retention following surgery on the anorectal region has been the theory of spasm due to the phenomenon of reflex pain. Since the bladder, urethra and supporting structures of the pelvic urinary system are innervated by the visceral branches of the second, third, and fourth sacral nerves through the pelvic plexus and since the branches of the same nerves via the pudic, inferior hemorrhoidal and dorsal nerve of the penis innervate the anal area and distal portions of the urethra, it has been reasonable to assume that reflex pain, spasm and inability to urinate would necessarily occur in a large number of patients.

Encouraged and stimulated to reject this theory by Dr. Richard A. Hopping of East Orange, New Jersey, whose experience on a large number of patients convinced him that the cause of urinary retention was to be found in a different theory, the author adopted Dr. Hopping's postoperative routine for anorectal surgical patients. One hundred and twenty-five consecutive patients were operated upon for the usual anorectal surgical conditions, and a bladder catheter for immediate postoperative urinary retention was used in only one case. This patient was a highly nervous and tense individual who was unable to cooperate.

The newly adopted routine consists of limiting intravenous fluids during the period of anesthesia to less than 200 cc. On the day of surgery the orders call for nothing by mouth except occasional sips of water. Early on the morning of the first postoperative day the patient is placed in a shower or tub bath and encouraged to void. The results have been uniformly successful.

In the light of our present experience it is logical to assume that urinary retention following anorectal surgery is due to bladder distention, or overdistention, in the immediate postoperative period and not due to reflex pain and spasm.

One hundred and twenty-four out of one hundred and twenty-five patients successfully emptied their bladders within twenty-four hours after undergoing anorectal surgery using the newly instituted postoperative routine.

William C. Bernstein, M.D.*
St. Paul, Minnesota

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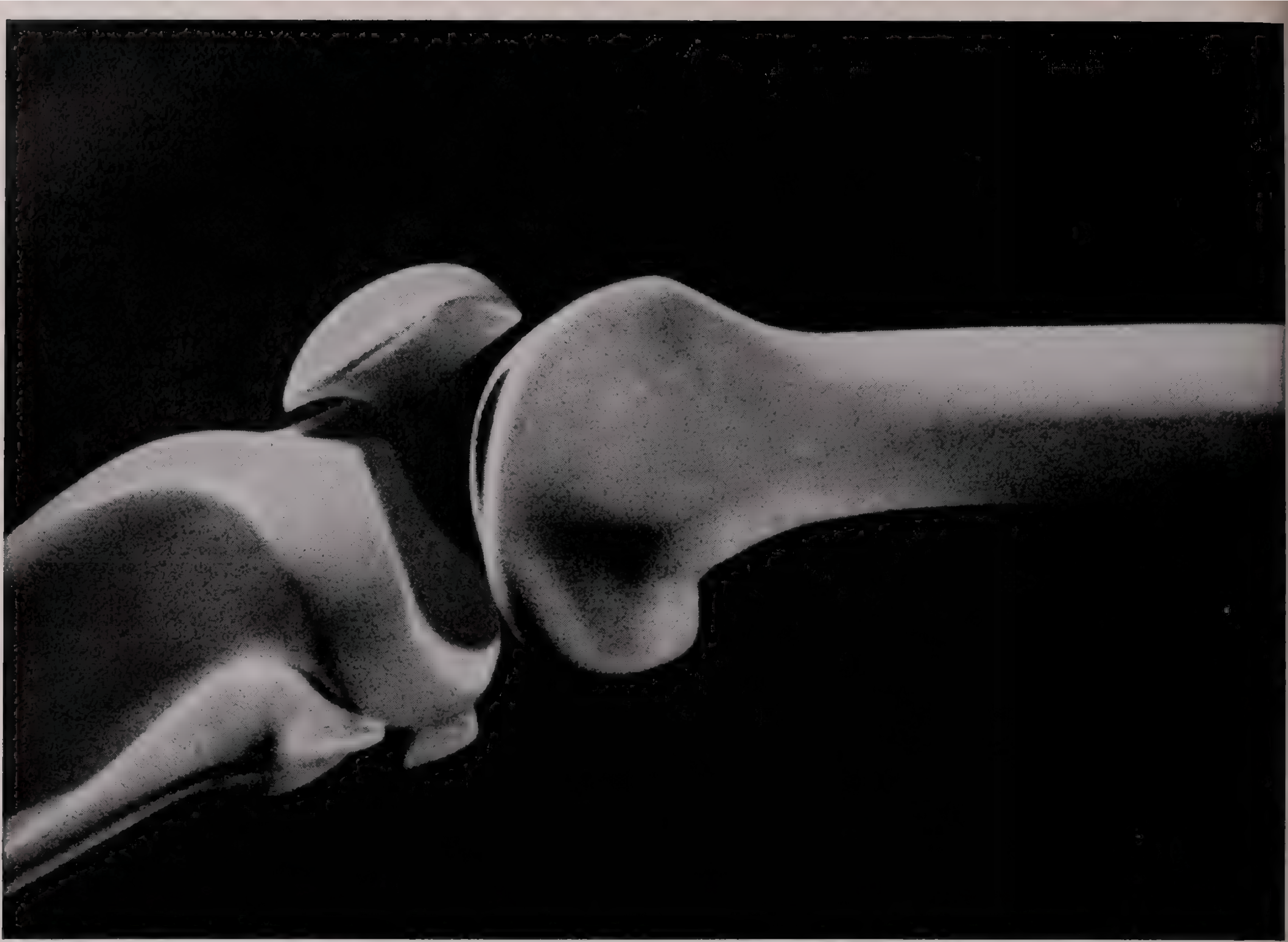
*Division of Proctology, University of Minnesota.



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Contraindications
Edema, danger of cardiac decompensation; history or symptoms of peptic ulcer; renal, hepatic or cardiac damage; history of drug allergy; history of blood dyscrasia. The drug should not be given when the patient is senile, or when other potent drugs are given concurrently. Large doses are contraindicated in patients with glaucoma.

Precautions
Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patient should be closely supervised and should be warned to report immediately fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools. Make regular blood counts. Use greater care in the elderly.

Warning
If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy.

Adverse Reactions
The most common are nausea, edema and drug rash. Hemodilution may cause moderate fall in red cell count. The drug may reactivate a latent peptic ulcer. Infrequently, agranulocytosis, generalized allergic reaction, stomatitis, salivary gland enlargement, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported but cannot definitely be attributed to the drug. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hepatitis, jaundice, and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently.

Dosage
The initial daily dosage in adults is 300-600 mg. daily in divided doses. In most instances, 400 mg. daily is sufficient. When improvement occurs, dosage should be decreased to the minimum effective level: this should not exceed 400 mg. daily, and is often achieved with only 100-200 mg. daily.

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Neuro-Pediatrics Conference

Retarded Speech*

Focal or Diffuse Cerebral Disease?

Dr. Edward Defoe**

This six-year-old boy was first seen at the University of Minnesota Hospitals August 7, 1962, for evaluation of developmental retardation, seizure activity and right hemiplegia.

Delivery was reported to have been uneventful following a full-term pregnancy and uncomplicated labor. Birth weight was 7 lbs., 11 oz. No significant neonatal illnesses were noted. Although neuromotor milestones are somewhat vague, the patient was said to have been somewhat slower than his sibs. He walked at 18 months and was neither toilet trained nor talking at three years when first seen at the University Hospitals. At 15 months he fell from his crib, striking his head; but this was not considered a serious fall. He had no loss of consciousness and no apparent complications, and he was not seen by a physician. The first generalized seizure occurred at 18 months. Seizure activity continued (mainly 15 to 20 minutes after going to sleep) in spite of Dilantin suspension (100 mg. per 4 cc.) ½ tspn. three times a day. At the time of the first University Hospital visit, the parents noted his irritability, clumsy gait, poor control of his right arm and leg, and some difficulty swallowing solid foods.

Physical Findings

Physical examination on August 7, 1962, accomplished with great difficulty because of the patient's apprehension, revealed an obviously retarded child with no speech, a grossly ataxic gait and a right hemiplegia. His head circumference was 49 cm. and his weight and height were just below the 15 percentile.

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*Held on Wednesday, October 6, 1965 at 1 p.m. in Hibbing, Minnesota.

Sponsored by the U. S. Public Health Service Grant N2502A63. These conferences are an integral part of the Comprehensive Clinic Program at the University of Minnesota Hospitals. The pediatric conferences are held weekly from 1 to 2 p.m. every Wednesday. The adult conferences are held every Thursday at 4 p.m. Co-ordinators for the project are Dr. Edward C. Defoe and Dr. Charles Branthaver in Pediatrics and Dr. Robert Soll in Adult Neurology.

**Pediatrician, University of Minnesota Hospitals, Conference Moderator.

Continued

Progress

An electroencephalogram revealed a spike focus in the left frontal area. Carotid angiography demonstrated right and posterior displacement of the left anterior cerebral artery. The left frontal lobe appeared quite avascular.

A left craniotomy was done for a suspected tumor. None was found. The brain in the left frontal area was quite firm with large overlying cortical veins and subarachnoid adhesions. The pathological diagnosis was diffuse gliosis with no evidence of neoplasia.

Following discharge on phenobarbital ½ gr. three times daily, he was seen again March 11, 1963. No further seizures were reported and he appeared to be using his right arm more. Head circumference was still 49 cm.

He was again seen August 10, 1965, because of parental concern over his retarded speech. At this time he was reported to have seizures occurring at approximately two-week intervals, with anticonvulsant therapy consisting only of elixir of phenobarbital (20 mg. tspn. twice daily). Most seizure activity had occurred approximately 15 to 20 minutes after he went to sleep. Although he is now toilet trained, he is unable to dress himself; he is able to speak only two or three words, preferring to point to objects. He continues to be apprehensive with strangers and covers his eyes when disturbed by loud noises or when confronted by strangers. Physical examination again revealed a frightened, retarded child with moderate spasticity of the right arm and leg. His weight and height were slightly below the 15th percentile. Head circumference was 49.5 cm. No speech was demonstrated.

Hemoglobin was 10.8 gm. The red cells were slightly hypochromic and microcytic.

Dr. B. French*

I did not see this boy until he was two years of age. He was noted to have a "flat head" at four months of age, and there is a note that "he should be watched closely." At 13 months a question of developmental retardation was raised by the pediatrician. However, no definite neurologic deficit was detected on physical examination. The diagnosis was "grand-mal epilepsy," which was treated with Dilantin ½ teaspoon three times daily. At the time of my last examination of him in January, 1962, he had poor coordination of the right arm and leg with a suggestion of ataxia, and I was suspicious of a lesion in the left hemisphere.

Dr. Michael Blaw**

In evaluating seizure patients one of our concerns is whether the seizures are a manifestation of an expanding intracranial mass and consequently whether contrast studies are indicated. Briefly stated the criteria used are: (1) Signs or symptoms of increased intracranial pressure; (2) Signs or symptoms of progressive neurological deficit, including behavioral, intellectual and seizure pattern; (3) Progressive slow-wave changes in the EEG.

Superimposed on the history of a boy with many stigmata of neurological deficits dating from birth was the story of the onset of a convulsive disorder. This symptom in itself might not warrant contrast studies if it were not for the history of progressive hemiparesis of recent onset. The pneumoencephalograms reveal that the anterior pole of the left ventricle is "cut off." The carotid angiogram shows avascularity in the area of the left frontal lobe. Both of these findings are consistent with a space-occupying neoplasm; hence, expectations were high that craniotomy would reveal a tumor. However, no tumor was found at the time of exploration.

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*Family physician.

**Pediatric neurologist, University of Minnesota Hospitals.

Dr. Defoe

Dr. Blaw, do you believe that these changes could have been secondary to the fall recorded at 15 months?

Dr. Blaw

No, I don't believe the two are related. The primary problem is most likely a cerebral anomaly unrelated to trauma. Of great significance is this boy's lack of speech. Speech development is usually centered in the left cerebral hemisphere. Although a left hemisphere lesion in a seven-year-old may produce aphasia, the entire left hemisphere may be removed prior to age three and still allow normal speech development. Speech function, therefore, is transferred to the right hemisphere under these circumstances. In this child the presence of poor speech development before the age of three would indicate either bilateral lesions or very diffuse brain involvement. He does indeed have indications of discrete involvement of his left hemisphere as manifested by his hemiparesis, but he also has evidence of diffuse involvement as suggested by his small head and intellectual deficit.

Dr. Defoe

Dr. Blaw, although this child's seizure problem temporarily abated after the initial hospitalization, the seizures are now severe, occurring every two weeks, and are of great concern to the parents. What recommendations do you have for medication?

Dr. Blaw

I note he has been on elixir of phenobarbital in rather small doses. I would suggest tablets be used instead. These can be crushed and given in a sweet vehicle of one kind or another. I would further suggest a phenobarbital dosage of 3-5 mg./kg. per day and dilantin 5-8 mg./kg. per day. Phenobarbital 15 mg. in the early morning, 15 mg. in the early afternoon, and 30 mg. one hour before bedtime in addition to dilantin 50 mg. in early morning and 50 mg. before bedtime would be a logical start. It will be extremely important for the mother to understand why these doses are necessary at the times prescribed, the importance of no omissions, and the importance of close contact with Dr. French for further dosage adjustment.

Dr. Harold Ireton*

I would ask whether this child's language problem represents a relatively specific aphasic disturbance or is but one reflection of more general mental retardation.

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*Psychologist, University of Minnesota Hospitals.

Continued

To communicate, he relies heavily on pointing or making facial gestures. His mother reports that this procedure is very effective at home ("there isn't a thing I don't know he wants," she says). He makes quick use of his mother whenever he is frustrated, and it is likely that she tries her best to help him at all times.

Intelligence and related testing was undertaken to document the generality and degree of retardation in areas other than language function which was his parents' specific focus of attention. On a battery of tests the boy failed to demonstrate functioning in any area beyond a four-year-old level. (He was six when tested.) On tasks requiring visual motor coordination, his performance was poorest (at about a three-year-old level).

His performance on cognitive tasks not requiring a verbal response and his rated social maturity would suggest an IQ of about 60, which places him within the educable range. However, such a "straightforward" classification is seriously compromised by his markedly inferior language skills.

The present evaluation indicates significant general mental retardation beyond impaired language skills. Further, his performance suggests that when he has to produce in a complex, coordinated fashion, as in the Goodenough, he is particularly deficient. Expressive language also depends on the ability to undertake complex coordinated activity in the production of speech.

Miss Helen Kretchmer*

The father is 16 years older than the mother. He has had 33 years of steady employment with the railroad. Both parents seem relaxed with the other children. Their main worries over the boy revolve around his seizures, his lack of speech, and his school placement. One or the other of them sits with him for an hour or so after he goes to bed, because this is the time he commonly has convulsions. Incidentally, he sleeps with his ten-year-old sister. This is also a precaution taken for early recognition of the seizures. This fear of seizure activity has undoubtedly been a major contribution to the mother's over-protectiveness of the child and certainly will add to her apprehension over letting him leave for a school setting. Although both parents are concerned over his lack of speech, the mother has probably done little to foster independence. Their understanding of the limitations and potential is probably not currently realistic and they will need continued gentle understanding support and guidance.

As a family, they go out very little. The parents are fairly well isolated at home with the patient. There are no relatives nearby. In addition to general medical advice and speech and school help for the boy, the mother also needs advice in daily living and instruction as to how the patient can be educated to help himself more.

Dr. W. F. Hunter**

It might be wise, in the area of self-help, to enlist the aid of Miss McCarthy who is a physical therapist here at the Hibbing Hospital. She undoubtedly could be most useful in setting up patterns for the mother to follow.

---

*Social worker, University of Minnesota Hospitals.

**Director, Range Mental Health Center, Hibbing, Minnesota.

Mrs. Judy Edmonds*

My initial speech, language and hearing evaluation was done on August 20, 1965. The boy is a rather hyperactive child and difficult to evaluate. His attention span is short, he is distractible, and it was difficult (but not impossible) to involve him in various tasks. Physically he is rather awkward. He used his left hand almost exclusively. He even operated a wastebasket foot lever with his left foot; he showed poor balance when asked to use his right foot.

The mother was extremely protective during the evaluation — jumping to pick up blocks he had dropped, helping him with puzzle pieces, and groaning when he made errors on language test items. She admitted waiting on him hand and foot at home, a fact which is probably partly responsible for his lack of social and self-help skills. (It was interesting that when I took him to the restroom he stood and waited for me to take his pants down or pull them up. When I suggested that he do it himself, he did so.)

Movements of his arms were occasionally jerky when he was asked to point to various parts of his body; but I was not sure whether this was due more to lack of physical control or to lack of certainty as to what he was to do.

Speech and Language Behavior

Receptive

His understanding of language was commensurate with his mental age. He followed directions involving prepositions "on," "under," and "over," but not "around." He knew most body parts but missed "foot" and pointed to his feet only when they were named. His response was not always immediate, which could have been due either to lack of understanding or to lack of cooperation. No formal test of hearing was made but as he followed directions given at a whisper without any visual cues, hearing acuity for speech sounds was adequate.

Expressive

He manipulated his environment and met his needs almost entirely by gesture. For example, he pulled at himself to show that he needed to "potty," pointed at things he wanted, etc. Usually gestures were not accompanied by any kind of verbalization. There was an occasional "uh" or "du" but not much more. He used the word "ball" several times, also "mom," "no," and "uh-oh." With those exceptions there was no vocalization. (He did make sounds for a pistol.)

The mother reported that she hears very little vocalizing at home, except an occasional "uh" when he needs to get her attention.

He was not persuaded to try any other words or any other sounds during this evaluation. His usual response was to go to his mother and whisper "du" in her ear. (Later he did this with me.) This was never vocalized and was nearly always the same consonant — "d." When we tried the "sh" sound, he puckered his lips but made no sound. His mother says he often uses this whispering in her ear at home. She thinks he is learning "good night" and "goodbye." The parents have not put much pressure on him to talk, but they think he is doing more vocalizing now than before. He has never done much babbling.

Continued

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*Speech therapist, University of Minnesota Hospitals.

Temporal Patterning

He copied two taps and three taps.

Peabody Picture Vocabulary Tests

He scored 37 (inconsistent pattern of errors) with a vocabulary age 3.7.

Motor Encoding Subtest of I.T.P.A.

His score was eight, which is at language age level 3.6.

Visual Motor

He had difficulty fitting simple puzzles together, did not copy block patterns of any sort, drew straight lines and circles at the third-year level of development, but did not copy the cross or the square.

Draw-a-Man (Goodenough)

This was essentially scribbling. His mother says he has not had much experience at home drawing or coloring. He plays outside most of the time. She says she thinks he can do better on drawing a man. Typically (at home) he draws a circle with eyes and nose and one ear. The other ear is elsewhere on the page.

Speech Mechanism

He controlled his tongue movements fairly well. Touch localization sensitivity of the tongue and lips was fairly good. He would not try to imitate any speech sounds; ability to do this should be further evaluated.

Auditory Discrimination of Noise Makers

Discrimination performance was inadequate but he may not have understood the task involved.

A further effort was made to evaluate his ability to produce speech sounds. With M & M reinforcers, he was persuaded to try and was able to produce vowels uh, oh, a, ah, and consonants b, p, t, l, m, and sh (without fricative components). He did not succeed in producing e, a, i, oo, or u. He imitated some pitch variation. He did much more vocalizing of vowel sounds this time than when last seen.

Summary

There are obviously many complex factors involved in this boy's lack of verbal communication. Partial motor apraxia and word aphasia are strong possibilities. Not to be ignored, however, is some lack of motivation to learn speech — imposed upon this boy's other problems. His hearing is adequate and his understanding vocabulary is commensurate with his IQ age. There appears to be nothing wrong with his speech mechanism. However, his expressive vocabulary is quite limited. There is little stimulation at home for learning speech. If he could have specific therapy (for example, the McGinnis "Association Method" would be appropriate) outside of the home for one-half hour daily, this would determine better the extent to which he can acquire an expressive vocabulary. A large amount of "reinforcement" for efforts will be important to the success of this type of training. Along with this, the mother can receive instruction in an approach which will promote acquisition of a receptive vocabulary to the maximum extent possible.

Concern was generally expressed that the boy is not ready for a regular school kindergarten environment because of his social, speech and general development limitations. Yet he badly needs stimulation from peer integration and a broader group experience for social reassurance. The best course for initiating his social debut in a manner least anxiety-provoking for the boy and his parents might be participation in a four-hour-a-day nursing school; or attendance in the Day Care Center in Chisholm would be a good alternative. Ultimate participation in special classes within the school system will necessarily depend upon progress noted within a more sheltered environment.

Dr. Defoe

This is a developmentally retarded boy who is functioning intellectually in the low educable range but who is further handicapped by lack of speech development, a hemiparesis, seizure activity and a continuing over-protective home environment. Better control of the seizures (through medication adjustment) will also come through social involvement in a protected nursery school or day care center and through specific speech instruction by Mr. R. Larsen.* More accurate judgement of the boy's ultimate potential for speech development and ultimate school placement must await such a trial period. Dr. B. French will continue to function as the primary physician responsible for medical management of the child and for continued guidance and support to the parents. University professionals will be available for further consultation when this is deemed appropriate by Dr. French and school personnel.

Addendum

Dr. Ward Darley has said (1) "*Medical Care*—concerns the functioning of our total medical establishment; all of its personnel and facilities and all organizational methods for the administration and financing of services; (2) *Patient Care* — while a part of medical care is the exchange and the results of the exchange that takes place at the level of the individual patient with his physician; (3) *Comprehensive Care* — is a system of person- and family-centered service rendered by a well balanced, well organized corps of professional, sub-professional and technical personnel who, by using facilities and equipment that are physically and functionally related can deliver effective service at a cost that is economically compatible with individual, family, community and national resources."

It is evident comprehensive care must encompass care which is optimally effective on a long-term basis, which means that one physician must have the primary responsibility for ongoing patient care. Yet there is a tendency in modern society to supplant this with episodic fragmented professional responsibility. Principal factors encouraging this relate to: (1) an increasing trend toward specialization, (2) increasing population movement, (3) the emergence of complex chronic disease which knows no clear-cut end point, and (4) increasing expectations of society for maintenance of health.

Dr. Lester Evans has stated in reference to comprehensive continuing care:[2] "There is nothing new or complicated in the concept. Basically, comprehensive medical care is the kind of compassionate personalized

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*Speech therapist, Hibbing Independent School District #701, Hibbing, Minnesota.

Continued

birth-to-death attention — preventive, advisory and rehabilitative as well as diagnostic and therapeutic — that the ideal family physician used to give (and sometimes still gives) within the limits of his knowledge and facilities.

What is new and complicated is adapting the concept to the uses of urban society and specialized skills; so that medical care does not become increasingly an episodic, impersonal and even haphazard matter of a patient's shopping in bewilderment from specialist to specialist, none of whom may know the emotional and environmental problems interacting with his organic complaint. The aim should be to combine the concentrated knowledge and skills of the specialists with the broad understanding, wisdom and continuing care of the generalist to the end that the patient receives precisely as little or as much care as he requires."

The principal aim of conferences such as this one held in Hibbing is encouragement within the community for the development of a true comprehensive approach to complex chronic problems. This approach must recognize the importance of close cooperative community effort, as well as effective utilization of other consultative sources, with retention of primary physician responsibility which promotes continuity of interest and involvement with the patient on a long-term basis.

Edward C. Defoe, M.D.
Conference Moderator

Those Participating in the Conference

Dr. B. French (family physician), Dr. W. Hunter (Director, Range Mental Health Center), Mr. R. Larsen (speech therapist, Hibbing Independent School District #701), Mr. Parker (Superintendent of Schools, Hibbing), S. Weinberger (Jefferson Elementary School, Hibbing), L. Seppi (special class teacher, Buhl), E. Stubblebire (Field Nurse State CCS for N. E. Minnesota) and other professionals from Hibbing and the surrounding communities. Mr. Blaw (pediatric neurologist), E. Defoe (pediatrician), J. Edmonds (speech therapist), H. Ireton (psychologist), and H. Kretchmer (social worker) from the University of Minnesota Hospitals.

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1. Darley, Ward, M.D.: Education for the Practice of Family Medicine. Address to the American Academy of General Practice, April 9, 1965 (unpublished).
2. Evans, Lester, M.D.: The Crisis in Medical Education, Ann Arbor, Michigan: The University of Michigan Press, 1964.

REITER'S SYNDROME*

Arthritis usually dominates the clinical picture of this syndrome with nonspecific urethritis, and conjunctivitis. There is acute pain, tenderness, swelling, heat, and effusion occurring in the weight bearing joints. This may be preceded by urethritis and conjunctivitis. The urethritis usually subsides within four weeks and the conjunctivitis continues for about ten days. There may be peripheral lymph adenopathy and cutaneous lesions resembling erythema multiforme. A viral etiology is suspected but no causative organism has been regularly demonstrated. The eventual prognosis is good and recovery is complete with ACTH cortisone producing dramatic results.

Durham, Robert H. — Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

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*See Grand Rounds, page 498.

Dentist: a prestidigitator who, putting metal into your mouth, pulls coins out of your pocket. — Ambrose Bierce

I have gout, asthma, and seven other maladies, but am otherwise healthy.
— Sydney Smith

Child Psychiatry

Behavior Problems and Cerebral Dysfunction in Children[*]

Part II

Diagnosis

Most physicians, well trained in a medical setting but lacking in training which only experience can provide, may feel insecure and yearn for an objective, structured approach when confronted with the responsibility for diagnosing and evaluating a perplexing behavior problem. The "whole child approach," so-called, is such a technique. It suggests one cannot consider a child's behavior as an entity in itself. It must be considered in the light of his physical health, his psyche, his emotional environment at home, school, etc. In brief, the physician's investigation should include:

1. The standard pediatric examination
2. Evaluation of the emotional status of the child and his environmental setting.
3. A functional neurological examination which concerns itself specifically with:
    a. neuromuscular function
    b. sensory function
    c. the sensorium
    d. possible history of impulse behavior
    e. intellect
    f. perception

The Standard Pediatric Examination

A considerable number of physical diseases in children present behavioral symptoms. An examination by a physician with pediatric diagnostic acumen is an essential part of the study of a behavior problem. For obvious reasons the practice of child guidance without benefit of a previous pediatric examination in the diagnostic study cannot be condoned. It must be an essential part of the total study.

Evaluation of the Emotional Status of the Child and His Environment

Medical practice provides us with a number of effective tools for this type of appraisal. Some of them are: the child's and family's cumulative observations concerning attitudes and feelings of the patient and members of the family toward each other and toward his staff during the periods of stress associated with disease. The attitudes and reactions of the child and individual family members toward the study of the "behavior problem" are likewise important. The failure of the father to concern himself about his child's predicament may be a significant indication of his attitude toward the situation.

Clearly, to use such tools effectively in the diagnosis and treatment in the area of feelings and attitudes, requires skills to observe, interview and communicate meaningfully with not only the patient and his parents, but

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[*] See Minnesota Med 49:305, 1966 for Part I.

Continued

also teachers, pastors, camp leaders and others who may be important in the child's environment. Such skills are not inherent in a physician; they have to be learned and developed. Unfortunately, formal training to observe, interview and communicate is not developed to any degree in the physician's and pediatrician's education. To acquire such skills requires initiative on the part of every individual physician. He must acquire the skills in question to deal effectively with the problem of the misunderstood child.

The Neuromuscular Examination

Observation of the child in active play is the most discerning test for revealing subtle neuromuscular functional deficiencies. In the office, it is excellent practice to observe how the child handles himself in play and ordinary activities. Such observations can be made in the waiting room or in the office, noting how the child plays or how he climbs on and off the examining table. He can be asked to skip and hop and to do several things at one time, such as extend the arms while closing the eyes and turning the head. In my own experience, except in the event of hyperactive knee jerks in the prone position and/or the inability to slide the heel of one foot down the shin of the other leg, the orthodox neurological examination has not been as useful as observing the child in action.

A comparative evaluation by an experienced, observing kindergarten teacher may be more helpful than a referral to a neurologist. The report of the former might read (as indeed one report did), "He has not yet learned to work or play with others satisfactorily. He is not cooperative or dependable with such things as putting on his clothes. Such skills as cutting and skipping are not yet mastered. His work habits are unsatisfactory, his drawing is little better than a scribble. He is interested in numbers and recognizes many." No committment was offered that a neurological deficit might explain such behavior.

Parent observations regarding neuromuscular function are prone to be unreliable.

Sensory Examination

The evaluation of sensory function is limited for all practical purposes to hearing and vision. An audiogram and Snellen test have been useful routines. An ophthalmological consultation is indicated if there is a question regarding vision, even in the presence of a normal Snellen. It is most damaging to the physician's rapport with a family when, later, a visual or hearing handicap that should have been revealed by the initial examination is noted. Thoroughness should be the watchword.

Sensorium Examination

Defects in the sensorium cause variation in the state of consciousness. Abnormal electroencephalogram tracings are seen in many children with brain injury but are also recorded in a significant proportion of "normal" children. An occasional child with unrecognized petit-mal epilepsy may be diagnosed by means of pathognomic encephalogram tracings; otherwise, in clinical practice it creates more problems than it solves. Based on my own experience I request an electroencephalogram only in a case of suspected petit-mal epilepsy. In three of my patients with previously unsuspected petit-mal, the clinical history on each case was most suggestive of the disorder.

Impulse Control

In the process of the child's maturation, an essential ingredient to satisfactory living is the development of impulse control. Fortunately most children learn this relatively early. Many children, however, with unrecognized cerebral dysfunction have difficulty mastering impulse control because of an inability to inhibit or delay response to environmental stimuli. They tend to have a short attention span, are easily distracted, engage in successive activities — often without completing a task, and tend to have difficulty when involved with large groups. Being unable to control their impulses, they are frequently in trouble in the classroom, playground and school bus. They lack the capacity to keep friends. It can be said they tend to do nothing in particular but what they do is done erratically.

In my experience this group of children lacking impulse control due to cerebral dysfunction demonstrated definite signs and symptoms of incoordination and distortions in perception.

One must always keep in mind the possibility that emotional tension due to excessive environmental stress may produce a similar lack of impulse control in other children.

Intellect and Perception

A clinical psychological consultation is desirable and often essential in evaluating intellectual, perceptual and academic achievement. It may also provide information regarding the emotional status of the patient. A good working relationship with his psychological consultant is essential for the physician. He must also be familiar with the various psychological tests in use to intelligently evaluate the psychologist's findings. Discussion with the psychologist is often necessary, as numerical and descriptive reports may require clarification.

The Working Hypothesis

When the diagnostic study is completed, the clinician has the task of equating and correlating the findings to plan a treatment program. A logical hypothesis of the dynamics of the problem requires a formulation. At this juncture the physician may ask himself, "Is this behavior problem a result of failure on the part of patients, teachers, etc. to recognize and accept a defect in the child's cerebral function?" If it seems so, the solution to the problem is to help the parents develop insight into and understanding of the child's deficiency. If, on the other hand, the neurologically handicapped child is reacting adversely to the tensions in his family, the possibility of psychiatric help must be considered.

The Therapeutic Test

If the diagnosis formulation is correct and the adults in the child's environment are adequate to develop an understanding and acceptance of the handicapped child, the problems in behavior are dramatically resolved — often permanently. In the severely handicapped child, situational problems at school will recur whenever school facilities are inadequate. These are most often understood and readily improved through the efforts of the school administrators without the physician being involved.

Continued

It is my observation that almost any kind of therapy directed at childhood behavior problems (regardless of their cause) may result in temporary improvement of behavior; however, nonspecific therapy does not result in the permanent solution of the problem. Arbitrarily, therefore, I have stipulated a three-year period of freedom from behavior problems when due primarily to an unrecognized cerebral dysfunction. Most children with a behavior problem related to more deeply rooted problems, often in the family, can be expected to have recurrent symptoms before three years have elapsed.

Prevention

Early diagnosis and interpretation of the child's handicap to the parents and teachers can be a real assistance in preventing those frustrating and embarrassing situations for the child which frequently develop into behavior problems. The child whose teacher is aware of his inability to skip and cut and draw can satisfactorily be spared the experience of repeated failures in this area. Many handicaps heretofore unrecognized, until a serious school behavior problem develops, can now be diagnosed in the preschool years and therapeutic measures instituted.

Treatment

The combination of understanding and acceptance by the adults dealing with the child is still the keynote of therapy. Interpretation is offered the parents according to their ability to grasp it. Fortunately, problems in the areas of neuromuscular activity, the sensorium, sensory perception, and cerebral perception are understood without difficulty. Problems related to impulse control are more difficult to deal with. Here the judicious use of the book, *The Other Child,*[1] may be helpful. The parents need to understand that the child requires firm, patient disciplinary support from them. They may get it from careful reading of this book and help from an understanding physician.

The beneficial results of environmental manipulation such as special schools transferring to smaller classrooms, avoiding such stimulating, unsupervised groups as are found on the school bus, the playground or in the lunchroom supplement parents' efforts in an effective way.

The conference between the physician and teacher has been an effective diagnostic tool as well as therapeutic device. The physician's objectivity is often helpful to the teacher, since he can often interpret the child to the teacher, thus increasing her understanding and acceptance of him and his limitations. It is unnecessary to ask special favors for the child. Such a conference, when it occurs in a stable school situation, invariably enhances increased cooperation between the school administrators and the parents. People in school administration are becoming increasingly aware of the needs of this group, and as a result, school resources are developing programs for their educational needs. Strauss and Lehtinen[2] deal thoroughly with the educational aspects of this problem.

A healthy on-going child-family-physician relationship is encouraged during and following the period of treatment. Parents of children with neurologic handicaps need a physcian with whom they can periodically consider their child's problems as new and different stressful situations develop.

Drug therapy can be judiciously used, always on an individual basis. In my own therapeutic program it plays a very minor role. Currently only four patients are on drugs: two on amphetamine sulfate, one on prochlorperazine, and one on reserpine. In my own experience, prolonged use of drugs is unnecessary. They may be useful on occasion for easing a patient and his family over a stressful situation, but the development of understanding and acceptance by parents is actually the only treatment that promises resolution of the problem.

One last word. In this, as in so many other areas of clinical medicine, the physician's attitude is a limiting and crucial factor in the area of diagnosis and treatment. Only if he is patient, sensitive, enthusiastic and hopeful about the possibility of improving the child's adjustment can he successfully influence other factors important in the child's every day life.

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The Blue-Glass Cure

Strikingly and pathetically naive among the many cures enjoying popular favor and testimonial endorsement in the last century was the blue-glass cure.

Because of a clerk's inadvertent blunder a glass-making firm was disconcerted one day to find itself with a large supply of unmarketable blue glass on hand. Anxious to dispose of this surplus without loss the firm offered a salesman a handsome bonus if he could contrive to sell the glass. Thus financially motivated, the salesman asked a scientific friend whether he could suggest any new uses for blue glass other than the conventional ones; to which his friend jokingly replied that since the blue end of the spectrum furnished actinic rays with photochemical properties, perhaps light rays through blue glass might possess some therapeutic value.

That was all the enterprising salesman needed! He proceeded to advertise the curatively-endowed blue glass so successfully that the supply promptly disappeared and the firm had to manufacture more blue glass to satisfy the local demand, which soon expanded into a national one, inducing other glass foundries also to engage in the lucrative manufacture of blue glass for multitudes of eager customers. Particularly gullible were Civil War veterans, both north and south, who alleged with conviction that naked exposure of their old wounds to the rays of light through the blue glass made the chronically bothersome aches and pains vanish.

In time, however, as the glass appeared to lose its potency, the craze waned. Disillusionment set in and the fickle public relegated its blue glass to the attic, from which, who knows, it may some day be resurrected, should some later generation decide to revive an earlier allegiance. Such revivals have been known to occur! Ironically, when the blue-glass craze was over, surplus blue glass again became "a drug on the market."

CO-GEL

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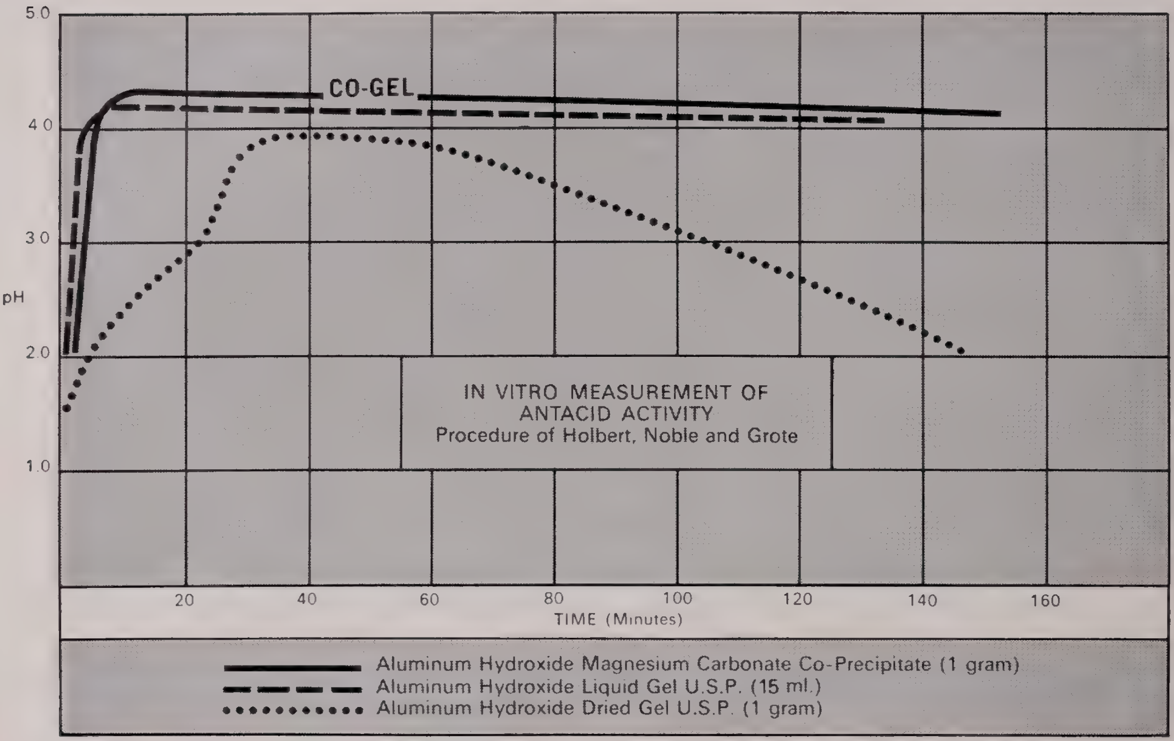

Holbert, J. M., Noble, N., and Grote, I. W.—Jnl. Amer. Pharm. Assoc. (Sci. Ed.) 37,292 (1948).

Now, an antacid tablet with the effectiveness of a liquid!

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The above chart compares the antacid action of the COGEL Tablet formula with both liquid and dry $Al(OH)_3$. Notice that CO-GEL neutralizes acid faster than $Al(OH)_3$ dried gel tablets and has a prolonged buffering action. The CO-GEL curve parallels that of liquid $Al(OH)_3$.

Liquid CO-GEL, containing the Co-Precipitate, is also available. CO-GEL is reasonably priced to the patient. Availability: CO-GEL Tablets (bottles of 100 and 1,000) CO-GEL Liquid (pints and gallons).

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Medical Seminar

The Penicillins

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PENICILLIN IS A generic term applied to an entire group of natural and semisynthetic antibiotics having a common nucleus, six aminopenicillanic acid (6-APA). These antibiotics have bactericidal action against many gram-positive and some gram-negative organisms. This group of drugs (1) has the same nucleus, (2) in general, shares cross antigenicity,* and (3) exerts its bactericidal effect in the same manner.

History of Penicillins

In 1929 Fleming, while at St. Marys Hospital, London, working on staphylococcal variants, noted that certain contaminating molds produced lysis of the staphylococci growing in cultures. He isolated the substance and named it penicillin after the mold producing it *(Penicillium notatum)*. With this substance, he conducted small-scale experiments in wound infections, but because of the small amount and crudeness of the product his work attracted little attention.

Penicillin remained of only academic interest until 1939 when Florey at Oxford launched the work that resulted in penicillin's application to clinical medicine. In 1940 Chain purified benzyl penicillin (penicillin G) from a substance produced by the mold, *P. notatum*.

An intensive developmental program was launched in Great Britain and the United States to develop the drug for use in World War II. Clinical trials were carried out at Yale and the Mayo Clinic in 1942 with encouraging results.[1,2] Further trials were conducted in the North African Theater of Operations in 1943, with success in the prophylaxis and treatment of wounds and in certain medical illnesses. Penicillin was rapidly accepted into the armamentarium of the armed services and was released for general clinical use shortly after World War II.

In 1945 Fleming, Florey, and Chain were awarded the Nobel Prize in Medicine for the development of penicillin.

In 1958 Sheehan isolated and produced the nucleus of the penicillin molecule, 6-APA. This opened the door for the chemical attachment of differing side chains and eventually resulted in the production of the new semisynthetic penicillins. In 1960 Doyle produced methicillin, the first semisynthetic penicillin active against penicillin-G resistant staphylococci.[2-4]

Classification of Penicillins

The penicillins may be divided into two groups: natural and semisynthetic. The natural penicillins are produced by the fermentation of the mold *Penicillium*, particularly *P. notatum* and *P. chrysogenum*. The semisynthetic penicillins are the result of chemically adding a different side chain to the 6-APA nucleus — the 6-APA nucleus being produced by the natural fermentation process; hence the term semisynthetic.

Natural Penicillins

The natural penicillins include: penicillins G, V, O, and N.

Continued

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*See Test Your Word Score Page 447.

Penicillin O is of interest because, originally, it was believed to have no cross-antigenicity with penicillin G and, therefore, would be of use in treating patients who were allergic to penicillin G. However, this has not proved to be the case, and penicillin O currently is of little clinical importance.

Penicillin N is a penicillin with a straight side chain rather than a benzyl side chain and is produced by the *Cephalosporium* organisms. Formerly known as cephalosporin N, it was renamed because it contained the 6-APA nucleus. The *Cephalosporium* organisms also produce substances with a slightly different nucleus from which the drug cephalothin (Keflin) has been derived.[3,5] There are other natural penicillins such as F, K, and X, currently of little clinical interest.

Semisynthetic Penicillins

These include (1) phenethicillin, (2) methicillin, (3) nafcillin, (4) oxacillin, (5) cloxacillin, and (6) ampicillin. To date more than 500 semisynthetic penicillins have been produced, a number of which are currently being evaluated clinically.

The Chemistry of Penicillins

The chemistry of the penicillins involves the nucleus 6 aminopenicillanic acid and a distinct side chain for each penicillin. The nucleus 6-APA is made up of a thiazolidine ring and a beta-lactam ring. The differing side chains seem to be responsible for the differing properties of the semisynthetic penicillins, including one or a combination of the three following characteristics: (1) acid resistance, resulting in absorption from the gastrointestinal tract, (2) penicillinase resistance, resulting in activity against penicillin-G resistant staphylococci, and (3) a broader spectrum of activity, with effectiveness against more gram-negative organisms.

Penicillinase is an enzyme produced by certain strains of *Staphylococcus* and *Bacillus cereus*, as well as other organisms, which acts to catalyze the enzymatic hydrolysis of penicillin G in opening the beta-lactam ring, producing penicilloic acid which has no antibacterial activity and which is relatively nonallergenic.[3]

Mode of Action of the Penicillins

The mode of action of all the penicillins in accomplishing their bactericidal effect is the destruction of the bacterial cell wall. The exact mechanism remains unknown but it seems to inhibit one or more enzymes, lead-

TABLE I
Natural and Semisynthetic Penicillins

Drug	Route of Administration	Indication
	Natural	
Penicillin G	Parenteral	Susceptible organisms*
Penicillin V (Compocillin-VK, V-Cillin, Pen Vee)	Oral	Susceptible organisms
	Semisynthetic	
Phenethicillin (Maxipen, Syncillin, Darcil, Ro-Cillin)	Oral	Susceptible organisms
Methicillin (Staphcillin, Dimocillin-RT)	Parenteral	Penicillin G-resistant staphylococci
Nafcillin (Unipen)	Oral, parenteral	Penicillin G-resistant staphylococci
Oxacillin (Resistopen, Prostaphlin)	Oral, parenteral	Penicillin G-resistant staphylococci
Cloxacillin (Tegopen)	Oral (parenteral not yet commercially available)	Penicillin G-resistant staphylococci
Ampicillin (Polycillin, Penbritin)	Oral, parenteral	Susceptible organisms, a broader spectrum of activity

*Susceptible organisms are gram-positive organisms excluding resistant staphylococci and including the gram-negative Neisseria.

ing to the accumulation of cell-wall precursors in affected bacteria. The penicillins thus inhibit the synthesis of essential cell-wall components or their assembly.

This is a fortunate fact of comparative histology; the substances making up the bacterial cell wall are highly vulnerable to penicillin, but the mammalian host cells are largely unaffected.[6]

Clinical Grouping

A clinical grouping of the penicillins of current importance is shown in Table 1.

Natural Penicillins

Penicillin G is still the most effective penicillin against *susceptible* organisms. Organisms against which penicillin G is the drug of choice are shown in Table 2.

Penicillin G or V, depending on the route of administration selected, is the drug of choice in the prophylaxis against rheumatic fever, endocarditis in valvular heart disease, lymphangitis, glomerulonephritis, and venereal disease.

Penicillin G is available in several forms: (1) aqueous crystalline for intravenous or intramuscular injection, giving rapid absorption and then excretion in three to six hours; (2) aqueous procaine, a repository form giving blood levels that persist from 12 to 24 hours; (3) benzanthine penicillin (Bicillin) for obtaining blood levels that persist from two to four weeks, and (4) PAM, procaine penicillin G in oil containing 2% aluminum monostearate, giving blood levels that last four days, used extensively by public health authorities in the treatment of gonorrhea and syphilis.

Penicillin G is also available in oral form, but its absorption is not as complete as that of penicillin V. Doses of penicillin G are varied with the organism and clinical situation and are, in general, well known. Currently, penicillin G is available primarily as the potassium salt with 1.5 mEq. of potassium present in each 1,000,000 units. As the sodium salt, penicillin G contains 0.1 gm. of sodium for each 1,000,000 units. These values must be considered in those patients with renal or cardiac disease or those receiving high doses intravenously.[7-9] Less well known is the effectiveness of penicillin G against some gram-negative bacilli, chiefly *Escherichia coli* and some strains of *Proteus mirabilis.*

The second natural penicillin of clinical importance is penicillin V. This drug is more effectively absorbed from the gastrointestinal tract than is penicillin G and gives higher blood levels which persist longer on oral administration than does penicillin G.[10] The absorption of penicillin V is not affected by the presence of food, as contrasted with phenethicillin. The acid-resistant quality of penicillin V gives it the advantage of being absorbed from the gastrointestinal tract. Therefore, penicillin V is used in mild infections in which the oral route is indicated. Studies[11] have indicated that it is effective in preventing endocarditis in valvular heart disease in patients undergoing oral surgery, when given in a dose of 500 mg. every six hours 24 hours prior to and continued for the 48 hours after surgery. Penicillin V in amounts of 125 mg. (200,000 units) or 250 mg. (400,000 units) given two to four times daily the first week of each month may prevent recurrent lymphangitis and consequent lymphedema. Usual doses are 125 mg. (200,000 units) every six hours for minor infections, and as much as 500 mg. (800,000 units) every four to six hours in more severe infections. Side effects include mild gastrointestinal irritation manifested by abdominal cramping and an increased number of stools that tend to be liquid.

TABLE 2
Organisms Against Which Penicillin G is the Drug of Choice

1. Diplococcus pneumoniae
2. Streptococcus pyogenes (beta-hemolytic streptococci)
3. Streptococcus viridans (Streptococcus mitis)
4. Enterococcus (Streptococcus faecalis) (when penicillin G is combined with streptomycin)
5. Staphylococcus aureus (nonpenicillinase producing)
6. Neisseria gonorrhoeae
7. Treponema pallidum
8. Neisseria meningitidis (intracellularis)
9. Fusospirochetes (Vincents')
10. Borrelia (relapsing fever)
11. Spirillum minus (rat-bite fever)
12. Streptobacillus moniliformis (rat-bite fever)
13. Clostridium
14. Actinomyces bovis
15. Bacillus anthracis
16. Listeria monocytogenes
17. Erysipelothrix insidiosa (erysipeloid)
18. Pasteurella multocida

Continued

In summary, the natural penicillins G and V are unsurpassed in the treatment of susceptible organisms and remain the drugs of choice in infections due to susceptible organisms: penicillin G parenterally and penicillin V orally.

Semisynthetic Penicillins

Phenethicillin was the first of the semisynthetic penicillins. It has the property of being acid-stable and, therefore, may be taken orally. However, food interferes with its absorption, as contrasted with penicillin V. Phenethicillin gives a higher blood concentration than does penicillin V but has no greater bactericidal effect, as determined by serum bactericidal tests. At the present time, phenethicillin acts essentially the same as penicillin V and thus may be used interchangeably, if the drug is given to a patient in the fasting state. The drug is appropriate for mild-to-moderate infections due to susceptible organisms, but it has no appreciable clinical effect on penicillinase-producing staphylococci. Phenethicillin is administered orally in a dose similar to that of penicillin V: 125 mg. (200,000 units), 250 mg. (400,000 units), or 500 mg. (800,000 units) by mouth every four to eight hours.

The first of four penicillinase-resistant semisynthetic penicillins (PRSP) to be discussed is methicillin. This drug was the first of the group of PRSP penicillins. Not being acid-stable, methicillin has two clinical properties. (1) It is not absorbed from the gastrointestinal tract and must be given parenterally; and (2) it should not be given in large volumes of intravenous solutions administered over several hours. The solutions may be relatively acid and the drug may be inactivated; therefore, if given in intravenous solution, it should be in 100- to 250-ml. solutions administered over one to two hours. Methicillin's main clinical use is against penicillin-G resistant staphylococci, which are defined as those requiring more than 1.0 μg per milliliter of penicillin G for inhibition. Methicillin is not inactivated by staphylococcal penicillinase, regardless of inoculum size. Against susceptible staphylococci, streptococci, and pneumonococci, methicillin has only about ⅓ the activity on a weight basis as has penicillin G. Methicillin has little effect against enterococci and no synergistic effect against enterococci when administered with streptomycin. The drug is less bound to plasma protein than are the other PRSP; but the significance of this is unknown. Some laboratory and clinical strains of staphylococci are resistant to methicillin; this has been noted in Great Britain particularly and on the European continent. As yet, clinical resistance has not become a serious problem in the United States.

The mechanism of steric hindrance has been proposed as the explanation of methicillin's resistance to penicillinase. This theory postulates that the inability of penicillinase to hydrolize methicillin and other PRSP is due to inability of the active sites of the enzyme to achieve sufficient contact with the specific groups of the penicillin. The methoxy groups attached to the benzene ring in the side chain of methicillin may be responsible for its steric hindrance.

Rare side effects of methicillin therapy include eosinophilia, neutropenia, and nephrotoxicity as manifested by proteinuria and hematuria. Overgrowth with gram-negative organisms has been a problem in some patients treated with methicillin.

The dose of methicillin is 1 to 2 gm. given intravenously or intramuscularly every two to six hours, with a maximal effective daily dose of 12 to 24 gm.

Nafcillin, oxacillin, and cloxacillin are similar in their clinical characteristics and effectiveness. These three semisynthetic penicillins have the same two qualities: acid resistance and penicillinase resistance. Therefore, they can be orally absorbed and are effective against resistant staphylococci. These drugs have biliary excretion and enterohepatic recirculation. Each has a higher serum protein binding than does methicillin, but the significance of this is unknown. The oral forms of these drugs give minor gastrointestinal side effects. When given orally, these drugs are absorbed best when the patient is fasting. Even in the fasting state, oral absorption is variable from individual to individual and is very poor in some patients.

Therefore, in serious infections the parenteral preparations of these drugs are preferred.

Nafcillin is more active against gram-positive susceptible organisms than is methicillin but, like oxacillin and cloxacillin, is still less effective than is penicillin G against susceptible organisms.

The same strains of staphylococci that are resistant to methicillin show increased resistance to these three drugs. (Thus far, this is not a clinical problem in the United States.)

Oxacillin is not excreted in sweat. Staphylococci may be cultured from pyoderma during treatment. Oxacillin's diffusion into serous cavities is poor.

Serum levels with cloxacillin are higher than those with oxacillin, but cloxacillin is eliminated more rapidly. Cloxacillin is only ¼ as active against pneumococci as is oxacillin.

The dosages for these three semisynthetic drugs are as follows: nafcillin, oral 250 mg. to 1 gm. every four to six hours, intramuscular 500 mg. every four to six hours, and intravenous 3 to 6 gm. per day; oxacillin, oral 500 mg. to 1 gm. every four to six hours, and intramuscular 500 mg. every four to six hours; cloxacillin, oral 500 mg. every four to six hours, and intramuscular 500 mg. every four to six hours. (Parenteral form is investigational at this time.) Oral forms should be given in the fasting state. In rare instances, oxacillin and cloxacillin may produce asymptomatic rises in serum glutamic oxaloacetic transaminase.

In summary, oxacillin, cloxacillin, and nafcillin given by the oral route appear to be equally effective clinically. Because these drugs are acid-resistant, they can be taken orally. They have biliary excretion and enterohepatic recirculation and have higher serum protein binding than does methicillin, but the significance of this is unknown. The oral products give mild gastrointestinal side effects.

Methicillin is not acid-resistant and must be given parenterally. Parenteral forms of oxacillin, cloxacillin, and nafcillin are approximately equal in clinical results to methicillin in the treatment of resistant staphylococcal infections.[12] These drugs are indicated in penicillinase-producing staphylococcal infections. None of these drugs (oxacillin, cloxacillin, nafcillin, methicillin) is as effective as penicillin G in the treatment of susceptible organisms.

Ampicillin differs from those previously discussed because (1) it is acid-resistant and, therefore, is absorbed orally, (2) it has a "broader" spectrum of activity, and (3) it has no effect against penicillin-G resistant staphylococci. It is only ¼ to ½ as effective against susceptible organisms as is penicillin G. Ampicillin is effective against some strains of *E. coli*, *P. mirabilis*, *Salmonella*, *Shigella*, *Haemophilus influenzae*, para-influenzal organisms, *Brucella*, and *Bacteroides*. The drug is not effective against the *Klebsiella-Aerobacter* group, *Pseudomonas* organisms, or some strains of *Proteus* (those that are indole producing). It has greater invitro activity against enterococci than do the other semisynthetic penicillins. Serum levels are not lessened when ampicillin is taken with food. The drug is not markedly bound to serum protein. Its concentration in bile is 300 times that in plasma. Ampicillin has a high biliary excretion and enterohepatic recirculation. Like penicillin G, ampicillin is inactivated by penicillinase and, therefore, has no place in the management of resistant staphylococcal infections. Chief interest in the drug has been in the management of (1) urinary tract infections, (2) enteric infections, including *Salmonella* carriers, and (3) chronic bronchopulmonary disease.[4] The dose is 500 mg. every four to six hours by mouth. The intramuscular dose recently made available is the same. Side effects include an asymptomatic rise in serum glutamic oxaloacetic transaminase in children.

The blood levels of all penicillins may be increased by the administration of probenecid (Benemid). This drug blocks the tubular excretion of penicillin by competitive inhibition: an important pharmacologic effect, since 80% of penicillin G is excreted by the renal tubule and only 20% by glomerular filtration. However, probenecid itself may cause hypersensitivity reactions.

Continued

Anaphylactoid reactions, fever, chills, rash, or anemia may be produced. The drug may also give a positive result to the Benedict test for reducing substance in the urine. Some patients are unable to tolerate the drug because of gastrointestinal irritation. Therefore, some physicians do not administer probenecid because it may confuse the clinical picture of the disease process itself or of the penicillin therapy. The usual dose is 0.5 gram by mouth every six hours.

Untoward Reactions

Allergy

This constitutes the most serious problem in penicillin therapy. Since all penicillins contain the 6-APA nucleus, if a patient is allergic to one penicillin, he may well be allergic to the others. It is estimated that allergic reactions occur in as many as 10% of patients receiving penicillin. The reactions include (1) skin reactions, (2) drug fever, (3) anaphylactoid reactions, (4) serum sickness, (5) toxic psychoses, and (6) hematemesis from urticaria of the gastrointestinal tract.

A recent study[4] found that the incidence of cutaneous reactions varied from 2.9 to 4.8%. In 793 cases of anaphylactoid shock, 72 deaths occurred, a 9% mortality rate.[4] Most likely to have a reaction are those who have received repeated doses, those who are in the 20 to 50-year age group, and those who have a history of atopy (hay fever, asthma, urticaria). The least likely mode of administration to cause a reaction is the oral; in one series, 0.5% reactions occurred. Intramuscular procaine penicillin was next with 1.4%, and intramuscular benzanthine penicillin was third with 3.8%. Topical penicillin is believed to produce the highest incidence of allergy.

When a patient is given his first injection of penicillin, he should be observed for 30 minutes after the injection; for symptoms of an anaphylactoid reaction usually occur within 10 minutes. Methods including skin testing, conjunctival testing, hemagglutination tests, passive transfer tests, and skin testing with penicilloyl-polylysine have all failed to detect those who later had serious reactions to injected penicillin. Also, even minute quantities of penicillin used in the testing solution have resulted in serious allergic reactions.

The treatment of an allergic reaction involves (1) adrenalin, (2) diphenhydramine hydrochloride (Benadryl), (3) penicillinase (may give an allergic reaction itself), (4) steroids (may be hazardous in a serious infection), and (5) maintenance of an adequate airway.

Penicillinase (Neutrapen) is produced from *B. cereus*. The dose is 800,000 units intramuscularly or intravenously, depending on the seriousness of the reaction, and may be repeated after three days. No more than three such doses should be administered during any one illness.

Toxicity

Direct toxicity to the mammalian host cells by the penicillins is rare and is manifested chiefly in the form of convulsions when very high doses are used (60 to 100,000,000 units per day). However, most normal patients can tolerate these doses.

Toxicity due to the salts contained in the penicillins is a hazard in patients with cardiac disease or renal disease or in those receiving high doses intravenously, as has been mentioned previously.

Indirect toxicity is present in two forms: (1) overgrowth with gram-negative organisms due to suppression of competitive flora, and (2) Herxheimer reactions that occur chiefly in the therapy of syphilis, resulting in chills, rise in temperature, malaise, muscle aching, and, at times, focal neurologic signs.

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Rochester, Minnesota

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3-12 May be secured from the author or the reprints.

Clinical Path Conference

Hemoptysis and Uremia

Case Report

A 61-year-old married white male was admitted to the Swedish Hospital on December 16, 1964, because of hemoptysis. One month previously he had experienced pain in multiple joints and was seen by his physician who made a diagnosis of acute arthritis. The joint pain was restricted to the hips and knees and was diagnosed as osteoarthritis. He was treated with sodium salicylate. Although his joint pain improved, he continued to have malaise and developed anorexia with a weight loss of 20 pounds. In retrospect, he stated that he had not felt well since a hemorrhoidectomy the previous July. His long-term complaints were fatigue, weakness, and malaise, and a slow decline in body weight. There was no story of previous hemoptysis, night sweats or fever.

Physical Examination

On physical examination he was pale with labored respirations. The blood pressure was 160/118, the pulse was 75 and regular, and the temperature was 98.5°. The patient's body showed the effects of weight loss. His heart sounds were normal without murmurs. Diffuse rales were heard in the chest, and the breath sounds were distant. No abdominal masses were felt. The abdomen was soft without tenderness. Peripheral and periorbital edema was absent. The joints were not tender, swollen, or deformed. There was no skin rash.

Laboratory

The laboratory studies included a hemoglobin of 7.4 gm%, a hematocrit of 23.5%, and a white blood cell count of 12,200 with 89 polymorphonuclear leucocytes. The peripheral smear was hypochromic and microscopic with moderate anisocytosis. Urinalysis showed a specific gravity of 1.010, 2+ albumin, 3-6 wbc/hpf, numerous rbc/hpf, and 14-18 granular casts/hpf. The stools were negative for occult blood. The blood urea nitrogen was 111 mg./100 ml. The sputum culture showed a moderate growth of *A. aerogenes.*

X-ray studies of the chest, gastrointestinal tract, and urinary tract were performed.

Course

The patient remained weak and anorectic and on December 18 had three episodes of coughing up small amounts of blood. On December 19 he became quite dyspneic, perspired and had a pulse of 112. His blood pressure fluctuated from 170/100 to 200/140. Because of continued dyspnea he was placed in oxygen. He continued to cough up blood-stained mucous and frothy fluid. He was given three units of packed cells for his anemia, but there was no change in his condition. He continued to perspire profusely and lapsed into coma. He died on December 21 — five days after admission.

Dr. Charles Kolars:*

Before I discuss the differential diagnosis, I would like Dr. Mork to give us his interpretation of the x-ray studies.

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*Attending internist, St. Barnabas Hospital.

Continued

Discussion of X-Rays

Dr. Frank Mork, Jr.:*

A film of the chest taken December 16 shows a diffuse mottled opacification of the left lung and a patchy area of infiltration in the right lower lobe (Figure 1). The costophrenic angles appear clear. I do not see any pleural fluid. The heart demonstrates left ventricular hypertrophy with a cardiothoracic index of 54%. The aorta is slightly ectatic. I see no masses in the chest and no hilar or mediastinal adenopathy. A repeat chest x-ray on December 19 shows no change in the left lung, but there is a progression in the right lung with mottled increased density occupying the right upper lobe (Figure 2). The costophrenic angles are still clear. There is no change in the heart size. A stomach examination was performed and was negative. An intravenous pyelogram was obtained December 19. The preliminary scout film shows the kidneys to be normal in size, shape and position. There is no calcification in the parenchyma. The intravenous pyelogram fails to visualize in three hours, indicating decreased renal function. The lung picture suggests several possibilities. One is a diffuse pneumonic process such as a fulminating gram-negative pneumonia. A further possibility is atypical pulmonary edema. This would fit nicely with the cardiac enlargement, but the lack of pleural fluid is against it. A third possibility from roentgen standpoint would be pulmonary hemorrhage associated with renal disease.

Differential Diagnosis

Dr. Kolars:

This is the case of a 61-year-old man who was admitted with evidence of renal disease and a rapidly explosive pulmonary picture with death five

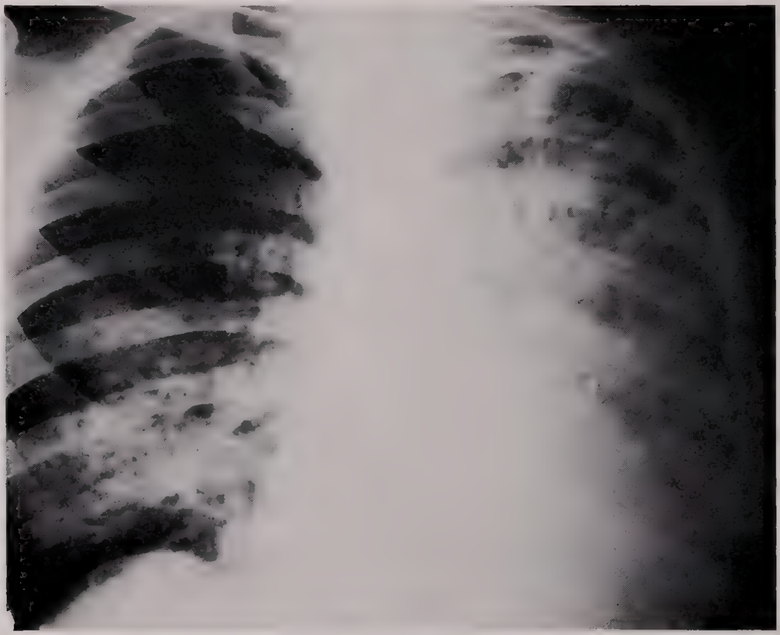

Fig. 1 — Initial film of chest taken on December 16th, showing patchy infiltration, most extensive in left lung. The heart appears slightly enlarged.

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*Radiologist, St. Barnabas Hospital.

days after admission. We have a hint that he had been in ill health for approximately six months. The exact characteristics of that ill health were not defined until about a month before his admission, when he had an isolated episode of arthritis. I assume the arthritis was not a recurring problem. The laboratory findings on admission indicate renal disease, and I would like to spend some time on this aspect.

Renal Disease

He had an elevated BUN and evidence of glomerulitis on urinalysis. The specific gravity is 1.010. This is probably a fixed specific gravity and indicates a severe degree of renal impairment. With the hemoglobin of 7.4 grams in the absence of any other blood loss one would tend to relate the anemia to chronic renal insufficiency.

I assume that the renal problem had been present for some time, but the normal-sized kidneys suggest that this has not been long-standing renal disease. It may be of several months' duration. Superimposed on the kidney disease is an acute pulmonary problem which spreads rapidly and leads to his death within five days.

Either this patient has a renal disease and a process in his lung which leads to his death or he has a systemic disease which is expressing itself in the lungs and the kidneys. I will leave the renal problem temporarily and concentrate on the pulmonary problem.

Infection

Infection is a consideration. The sputum was frothy and blood-tinged, and one culture showed a moderate growth of *Aerobacter aerogenes. Aerobacter aerogenes* is serologically indistinguishable from a *Klebsiella* or a Friedlander's type of bacillus. The genus of *Klebsiella* is felt now to include *Aerobacter.* Are we dealing with a severe Friedlander's pneumonia

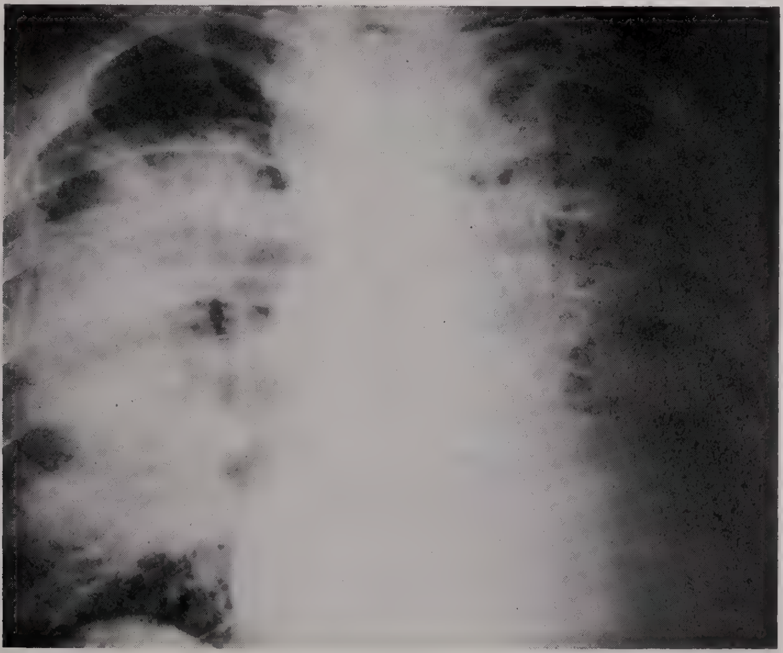

Fig. 2 — Film of chest three days after admission, demonstrating rapid progression of infiltration process into right lung and diffuse mottling of both lung fields.

Continued

which was rapidly progressive and superimposed on a pre-existing renal lesion? The film is against this. On the first film there is infiltration in the left lung with the beginning infiltration in the right (Figure 1). But three days later the left lung infiltration has not changed much. It remains the same, but there is an increase on the right side (Figure 2). If this were a Friedlander's pneumonia in its toxic progressive form, I would have expected further change in the left lung. Because the left lung remains relatively stable, because he is not febrile, and because he has a relatively low white count, I have to rule out infection.

Uremic Pneumonitis

Is uremic pneumonitis a logical diagnosis? Usually with the pneumonia of uremia, the BUN progressively rises and, in my experience, has been much higher than 111 mg./100 ml. and rising rapidly. Also, it is usually a diffuse process, and the left lung would not remain stable while changes in the right lung advanced. Is it pulmonary edema? If it were pulmonary edema I would have expected diffuse changes in both lungs.

Hemorrhagic Lungs and Vasculitis

Let's return to Dr. Mork's original suggestion of hemorrhage. This could account for the non-parallel changes in the two lungs. What could give the patient such a hemorrhage? A systemic process might involve both the lung and the kidney. Both a systemic vasculitis with involvement of medium and small blood vessels and an allergic or idiopathic vasculitis are possibilities. These may be expressed as specific disease entities such as periarteritis nodosa, Wegener's granulomatosis, or collagen disease such as lupus. Wegener's granulomatosis is unlikely because of the absence of a history of upper respiratory disease and purulent sinusitis. This disease is characterized by a generalized granulomatous vasculitis. It is usually initiated by a sinus problem and results in lung involvement and finally in renal failure. Periarteritis nodosa involving the lungs is almost invariably associated with an eosinophilia in the peripheral count, particularly if it involves the lungs to this extent. If it were a periarteritis nodosa, I don't think we could explain the rapid progression in this lung picture entirely on the basis of the nodular or vascular lesions.

Goodpasture's Syndrome

Another grouping vasculitis syndrome of more interest in recent years is Goodpasture's syndrome.[1] He had had a patient with pulmonary hemorrhage and renal glomerulitis who he felt had influenza during the pandemic of 1918-1919. This patient had an arteritis of the splenic vessels. The disease was resurrected in about 1958, and many cases have been described since. It is a disease which usually affects young males, but cases have been reported up to the age of 71 and down to the age of 13. It is a brief and fatal illness lasting anywhere from two weeks to three years, with the average being about six months.

It is almost always characterized by repeated pulmonary hemorrhages with hemoptysis. This is usually enough to produce an iron deficiency anemia. The anemia is attributed to a loss of iron into the alveoli, and pulmonary hemosiderosis is a common complication. This iron becomes sequestered and is not available for recirculation.

Renal disease almost invariably follows the pulmonary disease. There are cases on record in which the renal disease develops extremely rapidly. In one case the person went from a normal urine to a biopsy-documented glomerulonephritis within three months. Some patients are admitted with pulmonary infiltrates with the anemia down as low as 3 to 4 grams but with relatively normal renal function. They then lapse into terminal renal failure.

Does this patient have Goodpasture's syndrome? The fact that the renal disease precedes the explosive terminal lung changes is atypical. In most cases of Goodpasture's the hemoptysis is a forerunner of uremia. There is controversy as to whether this is a distinct entity or just another unusual expression of a systemic vasculitis. Formerly, periarteritis was thought to be a diffuse disease involving primarily the medium-sized vessels, leading invariably to death. We know now that some cases of "periarteritis" are really a hypersensitivity angitis and are reversible. Their expression may be limited to the lung and the kidney. Of the approximately 53 cases of Goodpasture's that have been reported, six cases had evidence of arteritis in other organs. There are other authors who contend vigorously that Goodpasture's is not a vasculitis because they rarely find evidence of arteritis in the hemorrhagic lungs. Whether Goodpasture's is an arteritis or a distinct entity involving only lung and kidney is controversial. In any case, the pulmonary hemorrhage usually occurs before the glomerulonephritis.

Summary

We have a 61-year-old man who has been ill for six months and who dies with lung and kidney disease. I think he had a nonspecific vasculitis. I will not label it periarteritis specifically. I think periarteritis nodosa is unlikely because of the absence of eosinophilia. Goodpasture's syndrome seems as good a classification as any, whether or not arteritis was present. Secondly, he could have had a simple subacute glomerulonephritis with a superimposed infection, but I consider this less likely. Other possibilities are lupus erythematosus or a malignant type of rheumatoid arthritis. In the latter, extensive lung changes may be present but there is usually more evidence of arthritis. This man really didn't have a characteristic type of rheumatoid arthritis. I think we are dealing with a pulmonary-renal syndrome with the basic pathological events being manifestations of a vasculitis with probable hemorrhage into the lung.

Dr. Kolar's Diagnosis: Goodpasture's Syndrome.
Dr. Philip Olson:*

There is one other situation where you get diffuse pulmonary changes — alveolar cell carcinoma. Although patients with alveolar carcinoma seldom develop sudden changes in the lungs, they do have sudden pulmonary hemorrhages. The statement about frothy, copious secretions suggests alveolar cell carcinoma. In this carcinoma, copious amounts of sputum are the rule. Pulmonary hemorrhages and pulmonary infarct also occur.

Dr. Lyle Hay:**

Did he have any vomiting in these last few days?

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*Radiologist, St. Barnabas Hospital.

**Director of Medical Education, St. Barnabas Hospital.

Continued

Dr. Richard Reece:*

No, there was some confusion originally as to whether he had hematemesis or hemoptysis. With the negative Guaiac, gastrointestinal bleeding was dropped from consideration.

Pathology Discussion

Dr. Reece:

I will start with the autopsy observations: This heart weighed 520 grams and showed left ventricular hypertrophy. It displayed mild arteriosclerosis but no occlusions. The lungs were very heavy. The right weighed 1000 grams and the left 900 grams. Both exhibited purplish discoloration on the pleural surfaces. They showed the watery froth of pulmonary edema, and the parenchyma had scattered patches of hemorrhages in all lobes. Microscopically, the alveoli were distended with blood and were filled with hemosideran-laden macrophages (Figure 3). Fibrin exudation and a necrotizing alveolitis were prominent. The reticulum stain showed disruption and fraying of the alveolar septa.

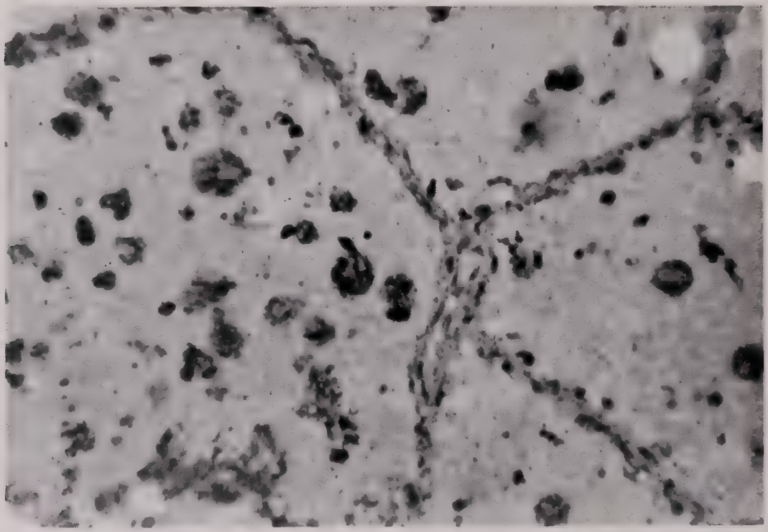

Fig. 3 — High power view of lung showing blood-filled alveoli and numerous hemosideran-laden macrophages.

The kidneys weighed 520 grams, were soft, flabby, and edematous and showed multiple punctate hemorrhages. The glomeruli demonstrated a subacute glomerulonephritis with epithelial crescents, fibrin thrombi, and thickening of the basement membrane (Figure 4). Multiple renal arteries and arterioles displayed a necrotizing fibrinoid degeneration with perivasculitis (Figure 5). Thrombi were present in medium-sized vessels in the renal pelvis and in a bladder vein but not in the major renal veins. A vessel in the periadrenal fat showed the typical picture of periarteritis. The splenic vessels and lung vessels were free of vasculitis.

Dr. Kolars:

May I ask one question: was there any evidence of arteritis in any other organs besides the bladder and adrenal?

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*Pathologist, St. Barnabas Hospital.

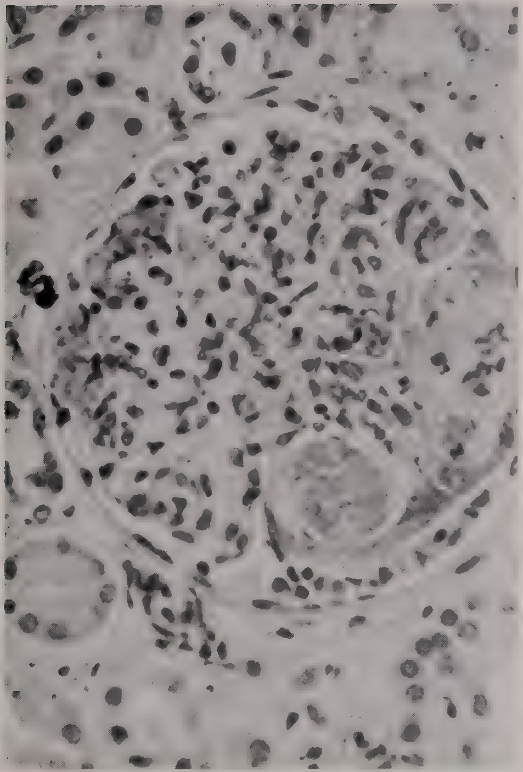

Fig. 4 — High power view of glomerulus demonstrating fibrin thrombi, cellular proliferation, and epithelial crescent formation.

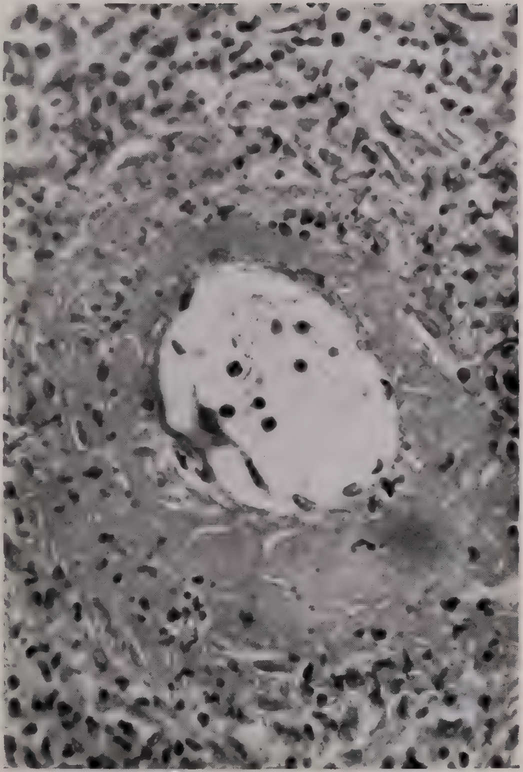

Fig. 5 — Renal vessel with smudging of wall and extensive fibrinoid necrosis.

Dr. Reece:

No, there was not. I might add that whether you call this Goodpasture's syndrome depends on how you define the syndrome. As Dr. Kolars mentioned, Ernest Goodpasture described arteritis in the splenic vessels and in vessels in the gastrointestinal tract. When Stanton and Tange rediscovered the syndrome in 1958, they said Goodpasture's syndrome was simply the combination of glomerulonephritis and pulmonary hemorrhage of obscure cause, and didn't mention the arteritis.[2] Then the ground rules were redefined and arteritis was excluded as part of the syndrome.[3] If arteritis is not part of the syndrome, Goodpasture's original case does not fit into Goodpasture's syndrome. Is this case a non-Goodpasture's syndrome, a poorpasture's syndrome, a Goodpasturoid syndrome or a Goodpasture's syndrome? I don't know, but I am going to accept Goodpasture's original case and call this case a Goodpasture's syndrome. A syndrome is supposed to be the sum of the signs and symptoms of any morbid process. This man had all the symptoms including hemoptysis and rapid fulminating death with uremia. He had a hypochromic anemia from his blood loss into his lungs, and he died within less than six months. It is true that he was not in the typical age group, but he had all of the other symptoms. As for pathological processes, he had the sum total of findings plus one — the arteritis. I think Dr. Kolars was correct. This is a Goodpasture's syndrome. But in scanning the literature, I reached the conclusion that Goodpasture's syndrome is probably just a manifestation of vasculitis, with the early changes not perceptible under the light microscope in most cases.

Continued

Dr. Kolars:

We agree that this is a muddled problem in classification and that we are dealing with a vasculitis. If Goodpasture's original case had evidence of arteritis in other organs, then I think we should attach the eponym of Goodpasture's to this case. This patient demonstrates the problems of trying to pidgeonhole diseases. This is because his case is not well understood. It is much better to accept it as a diffuse process which is expressing itself primarily in the lungs and kidneys.

Dr. Reece:

In the NEW ENGLAND MEDICAL JOURNAL there was a CPC case similar to this.[4] I like the way they summed it up. They called it an idiopathic pulmonary hemorrhage and subacute glomerulonephritis. Incidentally, we missed an important point in our discussion. Recognition of the syndrome is important because some patients can be salvaged with vigorous steroid therapy.[5]

Dr. Hay:

In just calling it pulmonary disease or chronic glomerulonephritis, you don't emphasize the underlying arteritis even if in this particular patient these were the only two organs affected. Do you think the arteritis in this particular entity is different from that seen occasionally in the intestines or other organs?

Dr. Reece:

I don't know.

Dr. Kolars:

The other curious aspect of the arteritis is that you rarely see it in the lung, isn't this right?

Dr. Reece:

Yes, and it was not present here.

Dr. Kolars:

You see it elsewhere, but you don't see it in the lung. This is one of the reasons that I think people have felt that it is a distinct entity rather than just an expression of a morbid systemic process.

Dr. Reece:

Some explain the affinity for just the lung and kidney damage on the basis of auto-immunity.[6] The lung serves as an antigen to the kidneys, initiating a hyperimmune glomerulonephritis. The similarities in the basement membranes in the alveoli and glomerulus lend some support to this concept.

Dr. Kolars:

If this were true, it would make it a distinct entity. The concept of a antigen antibody reaction in alveoli and glomeruli might also explain the response to steroids.

Final Anatomical Diagnosis

Extensive Pulmonary Hemorrhage and Subacute Glomerulonephritis (Goodpasture's Syndrome) Necrotizing Vasculitis of Periadrenal and Renal Vessels.

Richard L. Reece, M.D.
Minneapolis, Minnesota

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Gulliver's Travels — Jonathan Swift

During the troubled times of the early 18th century, Jonathan Swift, who deplored the numerous foibles of the human race, wrote a brilliant and biting satire designed "to vex the world rather than divert it." Publication of the manuscript was arranged mysteriously "by the odd expedient of dropping it at the door of a publisher from the window of a hackney coach." It would seem that many of the problems which disturbed Swift continue to remain with us and, as familiarly evidenced in our own society, would be well worth a review.

Gulliver — On Decision of the Supreme Court by Precedent

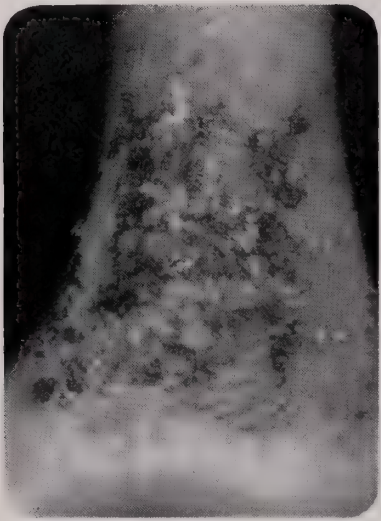
"It is a maxim among these lawyers, that whatever hath been done before may legally be done again: and therefore they take special care to record all the decisions formerly made against common justice and the general reason of mankind. These, under the name of precedents, they produce as authorities to justify the most iniquitous opinions; and the judges never fail of directing accordingly."

(To be continued)

Cabbage

Medicine has always provided an irresistible field for the activities of amateur physicians. One of the most interesting instances is the work written by Cato, the stern old Roman. He thought that cabbages were digested more easily than any other vegetable. They made a valuable tonic in vinegar. If you want to eat or drink copiously when you are invited to dinner, Cato advises you to take some cabbage in vinegar beforehand. When you have finished your repast and you want to eat again, it is sufficient to take about five leaves to have the illusion that you have not eaten for twenty-four hours. Cabbage is just as good externally as internally, being useful for trouble of the heart, liver, teeth, eyes, lungs, colic, cancer, abscess, and nasal polypi. . . . Above all, it was necessary to refrain from giving cabbages to slaves, — it made them eat too much. — Hubert Higgins: Humaniculture. Frederick Stokes Co., New York, 1906.

eczema: scourge of childhood



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Grand Rounds

Rheumatoid Arthritis in Children*

Rheumatoid arthritis is classified with the group of disorders known as the collagen diseases and, as such, presents a number of extremely difficult problems for the physician. Diagnosis is made by exclusion; prognosis cannot be stated with any certainty; there is no definitive cure for the disease, and the etiology is, as yet, unknown. To vividly illustrate how little real progress has been made in solving these problems, one has only to read Still's classic original article of 1896[1] and then survey the literature to the present to realize that rheumatoid arthritis in children remains almost as much of an enigma today as it was in Still's time. When viewed as a segment of the total arthritic population, children probably represent less than 5% of the patients;[2] however, to conclude from this that the disease rarely occurs in children would be erroneous. Available statistical data indicate that the incidence of new cases of rheumatoid arthritis is probably about 2.7 per 100,000 children under 16 years of age.[3] This figure is compared to the incidence of the nephrotic syndrome in children (2.3 per 100,000 under 10 years of age)[4] and of juvenile diabetes mellitus (less than 2.8 new cases per 100,000 under 15 years of age).[5]

Symptoms

Since by definition we are speaking of a disease which involves the joints at some time during its course, the other manifestations of what is really a systemic disease are often overlooked. Still's triad of splenomegaly, lymphadenopathy and arthritis are only three of many signs which can be characteristic, even if nonspecific, and may appear weeks or months before gross signs of arthritis appear.

Fever

Fever is very common. It may be spiking to 104 or 105 degrees or more

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*Presented as a Medical Grand Rounds at Mt. Sinai Hospital, Minneapolis, June 8, 1965.

Continued

chronic and low-grade; it may continue in spite of salicylate therapy and persist for months. During the fever the child may be restless and irritable, with a return to normal when the fever subsides. Frequently at the height of fever a characteristic rash will appear,[6] presenting as salmon-pink macules with pale centers, which spreads over the trunk but is usually concentrated on the skin overlying the joints. The rash generally disappears with the remission of the fever.

Carditis

Carditis occurs in approximately 10 to 20 per cent of cases and may be in the form of pericarditis, myocarditis, and valvular lesions with murmurs.

Subcutaneous Nodules

In the past the incidence of subcutaneous nodules in juvenile rheumatoid arthritis has been considered low.[2,7] However, recent studies[8] have described the frequent occurrence of nodules in children, which both clinically and histologically resemble the nodules of adult rheumatoid arthritis and occasionally those of rheumatic fever.

Weight Loss

Weight loss and anorexia are common and are probably manifestations of the systemic disease, as are the lymphadenopathy, splenomegaly and hepatomegaly, when present.

Joint Pain

The joint symptoms do not always begin as overt arthritis with swelling and warmth but may begin with intermittent pain in the joints in association with fever. Often the child indicates this pain by refusing to walk on an affected leg or to use an affected arm. When arthritis does finally present, it is characteristic in nature. Approximately 20%[9] of all cases will begin with a monoarticular involvement. Early in the disease there is periarticular swelling without fluid; the joint is warm but frequently not tender or red. The knee is the most commonly affected joint, the ankle and interphalangeal joints being next most common.[9-11] The cervical spine is also affected in a number of cases; Grokoest[10] found that pain and stiffness in the neck proved to be the most reliable symptom in the diagnosis of the disease.

Laboratory Findings

The laboratory tests are nonspecific and, as in the clinical findings, are of value only as part of a total picture. The most reliable, but also the most nonspecific finding, appears to be the sedimentation rate, which will be found to be greatly elevated. Most cases show a mild to moderate normocytic normochromic anemia, and in some a leukocytosis will be present. Increased C-reactive protein will sometimes be present during the acute phase of the disease. The latex fixation test shows poor reliability, being positive ony 10 to 20 per cent of the time. However, a more sensitive test for rheumatoid factor, the sheep cell agglutination inhibition test, has been more useful. In Toumbis' series,[11] in which he tested his patients for rheumatoid factor by sheep cell agglutination inhibition, sheep cell agglutination and latex fixation, the following results were obtained:

Serologic test for Rheum-factor	Number Studied	Number Positive	Per cent Positive
Sheep cell agglutination inh.	45	39	87
Sheep cell agglutination	45	18	40
Latex fixation	31	4	13

Although this is the only investigation presenting any data on the sheep cell agglutination inhibition test, the figures presented are impressive.

Therapy

Therapy in juvenile rheumatoid arthritis is really more a matter of management until such time as a remission takes place, rather than an attempt to cure the disease.

Analgesics and Anti-inflammatory Drugs

The basic therapy at present consists of analgesics and anti-inflammatory medications along with physiotherapy and psychological support. It is the usual practice to begin with salicylates in doses of 110 mgm. per kgm. per day, attempting to keep the blood salicylate level at 25 to 30 mgm%. If this fails to bring the desired symptomatic relief, steroids can be added and have been found effective in almost all cases.[12] Gauchat[12] reported a 50% success rate with Butazolidin, but this drug is infrequently used. Gold therapy also is still occasionally employed. However, a clinical remission is only the first step in treatment.

Physiotherapy

It is very important that a good program of physiotherapy be begun and maintained for as long as there is active disease, since mobility of the joints must be maintained in order to prevent joint deformities and flexion contractures. Although this may appear to be an insignificant part of the treatment, its real importance can be illustrated in a study by Edstrom[7] in which he showed the same therapeutic results in patients treated with bed rest and physiotherapy as in those treated with bed rest and also with salicylates, and steroids and physical therapy.

Prognosis

It is difficult to offer any kind of meaningful prognosis because of the great variability in the course of the disease. It may develop into a general systemic process, may be sustained through several complete and incomplete spontaneous remissions, may settle down to an indolent, painful arthritis with joint involvement lasting several weeks; or it may suddenly remit with complete recovery except for slight residual joint damage. In general, however, it can be stated that the prognosis appears to depend on when treatment is begun.[7,13] In Edstrom's series of 85 patients, the following results were obtained in patients treated early in their disease (one year or less):

Continued

State of Investigation	with	without	Total
	Chrysotherapy		
Recovered without defects	39 (63%)	14 (61%)	53 (62%)
Healed imperfectly	12 (19%)	4 (17%)	16 (19%)
Still progressing, crippled, dead	11 (18%)	5 (22%)	16 (19%)

Edstrom obtained similar results with patients placed on steroids early in their disease, illustrating once again the importance of instituting physiotherapy in an attempt to improve the prognosis.

Differential Diagnosis

A definitive diagnosis is most often made by exclusion and by the course of the disease.[14]

Rheumatic Fever

Rheumatic fever must be ruled out, and here differentiation may depend on the course of the disease. However, the following should be remembered: (1) rheumatic fever rarely occurs in children under five years of age; (2) the joint changes in rheumatic fever show severe pain, warmth and tenderness; and aspiration early in the disease will yield fluid; (3) the antistreptolysin titre will frequently be elevated in rheumatic fever; and (4) rheumatic fever will usually respond immediately and more completely to salicylates.

Collagen Disease

The collagen diseases, especially lupus erythematosus, must also be considered. The characteristic *lupus rash* is an important finding, and the patient may have signs of kidney involvement. The most specific tests would be the lupus erythematosus cell test and that for antinuclear antibody; but there is a certain degree of overlap between lupus and the other collagen diseases, as shown by Hall,[15] in a study of 130 patients with rheumatoid arthritis. In his series 98% had rheumatoid factor, but 13% had a positive lupus erythematosus cell test and 36% had antinuclear antibody. Dermatomyositis can present initially with joint symptoms but can usually be eliminated by electromyographic studies and the finding of an increased creatine excretion. On careful examination it will generally be found that the pain is adjacent to the joint rather than in it. *Periarteritis nodosa* can be a problem to differentiate when arthritis is the only symptom, because the vasculitis in the two diseases is similar. Leukemia can produce fever and joint pain before there is any abnormality in the peripheral blood.

Infection must always be considered. In the case of *pyogenic arthritis* the joint will show marked redness and inflammation. Diagnosis can usually be made by culture and smear of the synovial fluid.

Tuberculosis today is a rare cause of arthritis.

Occasionally, *allergy* may be the cause of arthritis and can usually be ruled out only by history. History should also rule out *trauma*. *Gout* is very infrequent in children. Reiter's syndrome* with urethritis, conjunctivitis and arthritis is also rare in children.

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*See Reiter's Syndrome page 472.

Etiology

As with any disease process the hope for a cure for rheumatoid arthritis doubtless lies in the discovery of its etiology, and this is where the greatest amount of work is being done today. There are three basic etiological theories: (1) the disease is infectious or microbial in origin; (2) it is genetically determined; (3) it is one of the "auto-immune" disorders.

Infection

Many of the proponents of infection as the etiological agent in rheumatoid arthritis base their contention on the finding of rheumatoid factor in patients with infectious diseases. Clinically, rheumatoid arthritis in children is often an acute systemic disease with sudden onset resembling a severe infection. Positive tests for rheumatoid factor have been found in syphilis,[16] leprosy,[17] tuberculosis,[18] measles,[19] viral diseases,[20] and subacute bacterial endocarditis.[21] Svartz[22,23] has shown that injection of rats with Group B streptococci can produce rheumatoid factor. Abruzzo and Christian[24] suggest that prolonged exposure to an agent might be operative in the pathogenesis of rheumatoid arthritis. The injection of rabbits over a six-month period with a suspension of formalin-killed E. coli produced a serum factor very similar to the human rheumatoid factor.

Immunologic Mechanism

It may appear at an early age when certain immunologic mechanisms which might otherwise be implicated in the etiology or pathogenesis of this disease are grossly deficient.[9] It has also been observed that patients with agammaglobulinemia frequently suffer from a disease indistinguishable from rheumatoid arthritis, indicating that the disease can occur in patients with grossly defective immunologic responses. This would make it seem unlikely that rheumatoid factor, excessive production of antibodies of gamma-globulin, or the production of auto-antibodies is responsible for the disease.[25] It is possible that the manifestations of hypersensitivity and auto-immunity may be secondary to primary infections; this would be consistent with the "self + x" theory of Lawrence.[26] In this theory, self is the host cell and "x" some outside agent existing within the cell; eventually cells of the leukocyte series are sensitized to this antigenic complex. If this theory proves to be a satisfactory explanation for delayed hypersensitivity, the nature of "x" becomes very important; "x" may be a virus or a pleuropneumonia-like organism.

Pneumonia-like Organism

The possibility that the etiological agent may be a pleuropneumonia-like organism has been suggested, since there is a similarity of pleuropneumonia-like urethritis and arthritis to rheumatoid arthritis.[27] It has been established that a typical pneumonia is due to a pleuropneumonia-like organism. This disease is associated with the appearance in the serum of cold agglutinins which, like the rheumatoid factor, are 19s gamma-globulins.[28]

The negative findings in the search for an infecting agent cannot

Continued

be overlooked. Using modern techniques attempts have been made to isolate pleuropneumonia-like organisms from the blood, synovial fluid and other fluids from these patients without success.[28] Synovial fluid from adults with classic arthritis and from children with severe fulminating juvenile rheumatoid arthritis, and blood from children septic with juvenile rheumatoid arthritis, and with agammaglobulinemia and arthritis have been inoculated intraperitoneally, intracerebrally, intravenously and intrasynovially into mice, rats, guinea pigs, rabbits and monkeys, and by similar routes into neonatal mice, rabbits and monkeys. In no instance has disease been produced.[28,29]

Genetically Determined

The hypothesis that rheumatoid arthritis may be genetically determined stems from the numerous studies that have shown a higher incidence of rheumatoid arthritis and rheumatoid factor in relatives of rheumatoid individuals than in the general population. In a group of four surveys the incidence of rheumatoid arthritis averaged 3% (2.1 to 3.8) in parent and siblings of patients with rheumatoid arthritis and 0.9% (0.7 to 1.8) in relatives of control individuals.[30-33] Ziff[34] found that a significantly greater percentage of siblings, parents and offspring of rheumatoid individuals gave positive tests for rheumatoid factor by the inhibition method (in one group) and by a capillary tube latex fixation method (in a second group) than was observed among simultaneously tested control individuals. In the first group 20% and in the second group 14% of relatives had positive tests, whereas only 5 and 1.4% of control subjects respectively reacted similarly. Lawrence and Ball[35] reported a fourfold increase in the incidence of clinical, radiologic and serologic evidence of rheumatoid arthritis when compared to the expected frequency as seen in a control group of adults. Toumbis[11] reported similar results in the relatives of patients with juvenile rheumatoid arthritis. Serologic tests using the sensitive sheep cell agglutination inhibition test on asymptomatic relatives of patients with juvenile rheumatoid arthritis showed 18% to have a positive serologic test, which was significantly higher than in the control group.

Auto-immune Phenomena

The group of investigators favoring the theory that rheumatoid arthritis is an auto-immune phenomenon believe that the question of the rheumatoid factor must be dealt with before we can understand the disease. The great majority of their work has been in demonstrating that rheumatoid factor is most likely an antibody-like substance directed against an altered gamma-globulin. Studies with two fluorescent reactants prepared for the detection of rheumatoid factor in situ in tissue sections[36,37] showed that cells which form the rheumatoid factor are plasma cells and are an integral part of the synovial inflammatory exudate in rheumatoid arthritis and occur in lymph nodes as well. The cells which produce rheumatoid factor belong to the same family of cells which produce antibodies, therefore suggesting an antibody-like nature and function for rheumatoid factor. If this is the case, a search should be undertaken in the tissues for the provocative antigen, such as an altered human gamma-globulin. In work with guinea pigs[38] and rabbits[39] it has been shown that antibody formation was stimulated when a chemically altered gamma-globulin was reinjected. Giving further support to the theory that rheumatoid factor may be auto-antibody and that an antigen antibody complex does exist in vivo in patients with rheumatoid arthritis is the demonstration by Taylor and Sheperd[40] of the reaction between autologous serum (containing rheumatoid factor) and some component, presumably gamma-globulin, in subcutaneous nodules of patients with rheumatoid arthritis.

Comments

A great deal of work in the area of auto-immunization has been done by Grubb, who demonstrated certain variations in human gamma-globulin termed Gm.[41] He suggests that rheumatoid factor is an antibody directed against Gm and calls it an anti-Gm. He has further shown that anti-Gm reagins may occur in normal persons or in persons with other diseases, although they are significantly much more common in rheumatoid arthritis.[42] Other investigators have presented evidence that anti-Gm reagins are characterized by many of the features typical of the rheumatoid factors[43] and that the most distinguishing characteristic of rheumatoid factor compared to anti-Gm reagins is its ability to react as an antibody with its own autologous denatured gamma-globulin.[44]

One of the major points in Still's original work[1] was that while rheumatoid arthritis beginning in childhood resembles the disease in adults in many ways, several differences, such as the high incidence of systemic manifestations, the rarity of subcutaneous nodules and the difference in the joints affected, would make it appear that the disease in children is different from that in adults. In addition, the low incidence of positive serologic tests for rheumatoid factor has been cited as evidence for a difference in the diseases. However, in recent years most investigators have recognized that these differences are minor and probably evidences of maturity.

The argument presented by Toumbis[11] is quite representative of the premise that these diseases are similar and that Still's disease is more properly called juvenile rheumatoid arthritis. One of the most striking differences in children as compared to adults is the high incidence of hepatosplenomegaly and lymphadenopathy. However, this probably represents a hyperactive reticuloendothelial system in children, since such findings are frequently encountered in many diseases in children. The likelihood of this is further borne out by the fact that the severity of the disease in children with hepotosplenomegaly is not significantly greater. In the Toumbis series subcutaneous nodules were found in six subjects and histologically resembled those in adults; in no instance were the nodules present before the age of nine, and three of the children were over 12 years of age when nodules first appeared.

The most convincing evidence that adult and juvenile arthritis are similar is made through serologic testing. Using the sheep cell agglutination inhibition test Toumbis found 87% of the children in his study to show positive tests for rheumatoid factor, while only 13% were positive by the latex fixation reaction. This is doubtless due to the fact that the immune response in children is less well developed, requiring more sensitive techniques to detect the presence of rheumatoid factor.

The final evidence presented is that related to serologic testing of asymptomatic relatives of the patients with juvenile rheumatoid arthritis. The

Continued

asymptomatic relatives showed an incidence of positive serologic tests by the sheep cell agglutination inhibition method approximately four times that of the control patients, and the incidence of 18% positive results was similar to that in relatives of patients with adult rheumatoid arthritis as recorded in another study.[34]

Case Report

A 13-year-old white male was admitted to Mount Sinai Hospital for the first time on 10/13/64 with a two-month history of migratory polyarthritis of the hips, knees and shoulders and a sedimentation rate in the range of 30 mm. in one hour. He had been treated with aspirin and penicillin with some relief. The past history and review of systems were negative; the physical examination with special attention to joint examination was normal at this time. During his hospitalization the patient's temperature ranged from 99° to 101° and the sedimentation rate from 40 to 63 mm. in one hour. The EKG and serum electrophoresis were within normal limits. The antistreptolysin titre was 0 and C-reactive protein was negative. Rheumatoid factor was not found. No lupus erythematosus bodies were present. The hemoglobin 13.0, WBC 7,200 with 59 PMN, 35 lymphocytes, 4 monocytes and 2 eosinophiles. Urinalysis: Sp. Gr. 1.020, pH 7, albumin 0, glucose 0, rbc 1-4, wbc occasional and casts 0. Uric acid: 3.4 mg%, Na 143 mEq/L, Cl 105 mEq/L, K 5.2 mEq/L, Ca 9.8 mg% and P 4.1 mg%. X-rays including chest, pelvis, ankles and shoulders were all negative. A diagnosis of acute rheumatic fever with the possibility of a mild rheumatoid arthritis was made, and the patient was discharged on prophylactic penicillin and aspirin therapy.

Shortly after his return home he once again began to have recurring attacks of acute arthritis in the wrists, knees and hips. Decadron 3 mg. per day was started and symptoms subsided. As the dosage was reduced over a four-month period to 0.75 mg. every other day his joint symptoms recurred, and he was readmitted to Mt. Sinai Hospital on 3/27/65. On physical examination at this time the patient appeared cushinoid. Except for a very minimal tenderness on flexion of the knee and slight tenderness over the left hip, the physical examination was within normal limits. On this admission the temperature remained in the range of 98 to 99°, and the sedimentation rate was 47. A diagnosis of juvenile rheumatoid arthritis was made and the patient was discharged on high doses of aspirin.

Alan Sinaiko
Medical Student
Mt. Sinai Hospital

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9-44 May be secured from the Grand Rounds Editor.

The Penalty of Overweight

Corpulence may lead not only to physical disorders, but to psychological aberrations. Fat persons may find themselves rejected by others, and also find that they are handicapped in many normal activities.

— Cyril M. MacBryde, M.D. Signs & Symptoms Lippincott Co.

Evolving Concepts in Vascular Surgery*

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THE PAST decade has produced a myriad of techniques and procedures available to the surgeon for the selection and treatment of patients with peripheral vascular disease. During the past five years, some semblance of order has been achieved, enabling the surgeon to more intelligently focus his selection and treatment with steadily increasing success rates. It is the purpose of this paper to emphasize a few of the evolving concepts.

Venous Disease

Superficial Saphenous Phlebitis

Superficial saphenous phlebitis is nonbacterial and requires no antibiotic therapy. This disease rarely, if ever, leads to pulmonary embolus, and anticoagulants are not required. In below-knee saphenous phlebitis the patient may be treated with a firm ace-wrap or elastic stocking and encouraged to walk or elevate his legs. When the phlebitis extends above the knee the patient is best treated with ligation of the saphenous vein at the saphenofemoral junction. This is accompanied by a marked decrease in pain. The amelioration of symptoms is presumably due to clotting the column of blood that is tamponading the phlebitic area. This procedure is performed with a small incision under local anesthesia. The patient may walk and go back to work. The pain usually completely resolves in forty-eight to seventy-two hours.

Deep Calf Thrombophlebitis

Deep calf thrombophlebitis is satisfactorily treated by the administration of heparin, followed by coumadin therapy. The route of administration of heparin is far less important than that it be adequately monitored. There is increasing awareness that large doses are required early in the treatment when the phlebitis is most active. In patients in whom heparin is contraindicated, superficial femoral vein ligation has proved to be a very satisfactory method of management. Patients who have emboli following adequate heparin therapy should be treated by venous ligation or plication, the level of which will be discussed later. At present the sedimentation rate is the only laboratory test of value in following the course of this disease. Coumadin therapy should be continued for three months.

Ileofemoral Thrombophlebitis

During the last ten years, the major advance in the treatment of ileofemoral thrombophlebitis has been prevention of the postphelebitic syndrome. The original procedure to remove clots from veins dates back to the work of Schepelmann in 1910.[1] Mahorner, in 1954,[2] revived interest in thrombectomy in this country.

Numerous reports are now available showing the beneficial effects of thrombectomy. The incidence of severe postphelebitic sequelae is 50% with heparin therapy alone

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*Presented before Minneapolis Academy of Medicine, February, 1965.

and drops to 10% with thrombectomy and heparin. Pulmonary embolism occurs in 10% of patients with ileofemoral thrombophlebitis treated with heparin alone. With thrombectomy plus heparin the incidence drops to 1%. The efficacy of this procedure used early in the course of the disease continues to be well established.[1,3]

Treatment of Pulmonary Embolism

Venous Plication

Patients on heparin therapy who develop pulmonary embolism should undergo venous ligation. There has been a recent interest in venous plication, which leaves small channels available for continued blood flow and yet acts as a trap for any lethal clots. Whether a vein should be ligated or plicated remains to be determined. The single important factor is that venous interruption be performed to prevent further embolism. Inferior venacaval ligation gives almost one hundred per cent protection against further pulmonary emboli.[4] Bilateral common femoral vein ligation is accompanied by a ten per cent incidence of recurrent pulmonary emboli. It should be noted, however, that many patients who develop pulmonary emboli are extraordinarily poor operative risks due to cardiac or associated disease. Consequently, the lesser procedure may be indicated. In our own patients, persistent swelling following bilateral common femoral vein ligation or inferior venacaval ligation is seen in three and five per cent respectively.

Pulmonary Embolectomy

Since the original description by Trendelenburg[5] of pulmonary artery embolectomy, few successes and numerous failures have occurred. This has led to an interest in pulmonary artery embolectomy utilizing cardiopulmonary bypass. Successful management of acute massive pulmonary embolism rests on cardiovascular support, either by partial bypass or by immediate embolectomy, or both. Support of the failing cardiovascular system is imperative. From that point on, whether or not cardiopulmonary bypass is necessary to remove the pulmonary embolus has not been fully evaluated. There is no question but that cardiopulmonary bypass will allow a more thorough evacuation of clot from the pulmonary arteries. However, to tide the patient over the acute episode, immediate thoracotomy, with removal of the large plug of clot from either the main pulmonary artery, or from the right or left main pulmonary branches, is certainly life-saving. It should be kept in mind that a heart-lung apparatus is not imperative for a successful outcome in pulmonary embolectomy.[6,7]

Arterial Disease

Coronary Artery Disease

The diagnostic technique developed by Sone of coronary angiography is a major advance in the evaluation of coronary artery disease. This procedure, which has a low mortality, enables a much more careful evaluation of the coronary arterial tree. Typical of any dye injection studies on arteries, it is fraught with the problem that, despite anterior, lateral and oblique views, the dye may completely fill the lumen of a vessel and not show major disease that is present on one wall of the vessel. The same problem is commonly seen with aortography where the tremendous back-wall disease may not be delineated clearly, as the dye renders the aortic lumen opaque and the partially occluding back-wall disease is not seen. With any dye study the vessels always look better than they are.

Of the available procedures for persistent angina in coronary occlusive disease, endarterectomy, which is applicable in five per cent of patients with severe angina, has been followed by a high incidence of reocclusion. The procedure of endarterotomy,* which is opening the artery and putting on a vein patch without endarterectomy, as recently advocated by the Cleveland Clinic, is probably preferable. Further studies are beginning to show an increased long-term patency rate.

Vineberg has had a continuing experience with the internal mammary artery implant procedure. This procedure is applicable only to anterior-wall disease; at the present time there is no standardized procedure for posterior-wall disease. Internal mammary artery implant is performed with a sixty-four per cent good result in Vineberg's hands.[8] Vineberg recommends coronary angiography in all patients with persistent angina. Patients with occlusion of only one branch of the coronary artery are not operated upon, and time is allowed for them to develop their own collateral circulation. Patients with two arteries involved, for example, the anterior communicating and the right coronary, are advised to undergo internal mammary artery implantation in the hope of revascularizing the anterior wall of their left ventricle. Patients with three-vessel involvement or cardiac failure due to coronary artery disease are advised to undergo epicardiectomy* with removal of the serous pericardium, followed by wrapping a free graft of omentum about the heart and root of the aorta. This procedure has been successful both in animals and in humans in achieving some revascularization of the entire heart. Vineberg's results are certainly very encouraging, especially in view of the fact that medical measures have little to offer these patients at the present time. Several other procedures are being evaluated. The dissatisfaction with the presently available procedures lies in the fact that myocardial revascularization is not immediate, but rather requires up to six months or longer after operation.

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*See Test Your Word Score Page 447.

Extracranial Cerebral Vascular Disease

It is now established that patients with intermittent symptoms due to extracranial vascular occlusive disease can be safely carried through surgery and given a prolonged survival rate, free from stroke. Patients with progressing stroke, or completed strokes, are not as good candidates for this procedure. There are several reports of marked improvement in their condition; however, statistically valid figures are, to my knowledge, lacking at the present time. The major problem in the acute stroke is that of hemorrhage into the infarcted brain upon revascularization of the infarcted area. This occurs in approximately fifty per cent of acute strokes.

Several safety factors have been introduced into surgery on the extracranial vessels. These factors are primarily related to conduct of anesthesia as so aptly described by Wells and his associates.[9] Studies by Champ Lyons[10] suggest that general anesthesia may decrease the metabolic rate of the brain by as much as fifty per cent. Consequently, general anesthesia in and of itself may afford some protection to these patients during complete occlusion of their carotid artery. High oxygen flow using fluothane in a closed system can increase the arterial oxygen saturation to 450 mm. mercury partial pressure. Hypercarbia, created either by hypoventilation or five per cent CO_2 and oxygen, does dilate the cerebral vessels and increases cerebral blood flow by 30 to 38%. Sustained elevation of blood pressure, using vasopressors to increase the pressure over the patient's normal range, has been shown to increase the arterial pressure distal to an occlusive lesion. This increased pressure is most important in pushing blood around the circle of Willis which may have associated disease in these patients.

Patients with bilateral disease can be safely carried through surgery under hypothermia with its added protection and the utilization of intra-arterial bypasses during the time of carotid occlusion. Monitoring of jugular vein oxygen saturations during surgery, as recently described by Champ Lyons,[10] reveals that patients with a jugular vein oxygen saturation of 60% or lower should have intra-arterial bypasses inserted to prevent damaging ischemia. Such protection is unnecessary, however, if the jugular vein oxygen saturation is over 60%. Electroencephalogram monitoring likewise is efficacious in this regard and adds another method of operative monitoring that leads to increased safety for the patient. The high incidence of aneurysmal dilatation of vein patches when the jugular vein is used has led us to the use of only saphenous vein as a source of vein patches in arterial surgery. Frequently we use no patches but rely on 6-0 Tefdak or silk for closure of the arterotomy without constriction.

At the present time the problem cases are

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*See Test Your Word Score Page 447.

those of multiple vessel involvement and acute stroke. Careful selection of cases, accompanied by the use of the protective measures mentioned above, can carry these patients through surgery successfully with an excellent chance for good results.

Patients with innominate and subclavian artery take-off problems, demonstrating the subclavian steal syndrome, may now be operated without thoracotomy by utilizing carotid to subclavian bypasses. Many of these patients are not candidates for thoracotomy, and the ability to safely increase the distal subclavian artery pressure and stop the stealing of blood from the basilar-vertebral system by a well tolerated operation within the confines of the neck is a great advantage.

Renal Artery Hypertension

Among all the hypertensives in the United States the number of patients with renal artery hypertension is approximately one to five per cent. Congenital fibromuscular hyperplasia is the lesion of choice to treat, providing it does not involve the intrarenal vessels. A renal arterotomy and onlay of a saphenous vein-patch graft carry a success rate in the range of ninety per cent. Unfortunately, only thirteen to fifteen per cent of the renal arterial lesions are due to fibromuscular hyperplasia. Patients with renal artery atherosclerosis — unilateral or bilateral, whose affected kidneys are greater than ten centimeters in length, are amenable to renal arterial reconstruction with approximately an eighty per cent success rate. This represents a considerable salvage of kidneys. The twenty per cent of renal arterial reconstruction patients who fail may still have nephrectomy. The ten per cent of patients who are not cured by reconstruction or nephrectomy usually have irreversible vascular changes in the opposite kidney. As long as 18 months after renal arterial reconstruction, however, the blood pressure may still be diminishing, as the disease in the nonaffected kidney is reversed.

The status of this field of vascular surgery is certainly at the point where all patients, with the onset of hypertension under the age of thirty-five or over the age of fifty-five, should have aortographic evaluation of their renal arteries. Twenty-five per cent of these patients will have renal artery pathology. Many patients between the ages of 35 and 55 will have renal arterial lesions. However, case selection is necessitated prior to recommending aortography in these patients. The dehydrated and rehydrated intravenous pyelogram is ninety per cent accurate in revealing renal arterial lesions; consequently, a preaortography screening test is available to all patients with hypertensive disease.

We have all seen patients who have not responded to correction of their renal arterial lesion. Likewise we have seen patients who have disease in the smaller branches of the renal artery, which is not at this time amenable to surgical correction. Case selection still exists, even though a renal artery occlusive lesion is present.

Aortic Aneurysms

The nonhypertensive relatively young patient with an aortic aneurysm is no longer a problem. The problem patients are the elderly hypertensive patients with benign nephrosclerosis and coronary arterial disease. These patients need all the protection available to carry them through surgery. Protection of the kidneys is afforded by perirenal arterial sympathetic bloc with xylocaine and the use of mannitol during the procedure to continually wash out the kidney tubules. The proximal aorta is very carefully flushed to get rid of any debris or clots which may be present prior to final insertion of the graft. If possible, correction of renal artery stenosis by bypass or endarterectomy should be done at the same time as resection of the abdominal aortic aneurysm.

In order to protect the heart from coronary insufficiency and arrythmia, the following procedures are beneficial:

1. The use of preclotted graft minimizes leakage through the graft wall following release of the aortic clamps.
2. Installation of twenty milliequivalents of sodium bicarbonate into the graft prior to the release of the aortic clamp helps alkalinize the markedly acidic blood present in the distal extremities. We have found, as Vetto

reported,[11] that the PH of iliac vein blood after forty-five minutes of aortic occlusion averages 7.1. With the use of sodium bicarbonate instilled into the graft prior to declamping, the PH of iliac vein blood is elevated to 7.3. The arteriosclerotic human heart, unlike the dog heart, is susceptible to a rapid coronary infusion with low PH blood.

3. A vasoconstricting agent instilled into the graft prior to declamping causes peripheral vasoconstriction and decreases the usual peripheral vasodilatation accompanying the hyperemic response.

4. Over-transfusion by one unit of blood prior to declamping allows for vascular bed changes and graft oozing.

Utilizing the aforementioned procedures, the average pressure change following slow release of the aortic clamp is in the range of five to ten mm. of mercury. This is in contradistinction to the 30 to 50-mm. of mercury change in pressure when these procedures are not utilized. Arrhythmias and coronary artery insufficiency leading to ischemia and infarction have not been a problem in our hands following the institution of the abovementioned procedures.

The severely emphysematous patients continue to present the greatest risk in aortic surgery. With the wide exposure necessary, accompanied by some ileus, the diaphragmatic breathers are definitely in danger of pulmonary insufficiency postoperatively. Positive pressure breathing with good tracheal toilet and bronchodilators have markedly influenced the postoperative course in these poor risk patients.

Aorto-iliac Occlusive Disease

Patients with aorto-iliac occlusive disease are on the whole approximately ten years younger than patients with femoral-popliteal arterial disease. In this younger age group it is far preferable not to place a foreign material, the status of which ten or fifteen years later would be unknown. The long-term follow-up in some series[12] shows endarterectomy to have up to a 40% incidence of recurrent atherosclerosis in the endarterectomized segment. However, a different type of endarterectomy, where the entire media is completely removed out to the adventitia, shows a high success rate in the long-term follow-up, greater than that of bypass graft and free of recurrent atherosclerosis.[13,14] Consequently, we favor endarterectomy with venous onlay patch graft in those patients who are in the fifty to sixty-year age group or younger, providing their arteries are not heavily calcified. In the older age group bypass graft is satisfactory, shortens the procedure, and is indicated when marked calcification is present.

Femoral to Femoral Bypass

The high operative risk patient with claudication or ischemic ulceration due to unilateral iliac disease, is best treated at the present time by the Vetto femoral to femoral subcutaneous bypass graft under local anesthesia. A 95% success rate can be assured with this procedure. The good leg is not jeopardized and there is no postoperative claudication in the good leg. We have used this in patients who have superficial femoral artery disease on the good side, without the good leg being threatened. There has been no incidence of claudication in the twenty-nine cases performed to date in the good leg. There has been one late occlusion. It is now widely recognized that an absent femoral pulse is usually due to iliac or aorto-iliac disease, and the common femoral artery is usually patent if the leg is viable. A good input of blood into the common femoral artery will allow ischemic ulcers to start healing and, depending on run-off, will inhibit claudication. After femoral to femoral bypass patients with superficial femoral arterial disease or disease of the tibial vessels may not go on to completely heal their ischemic ulcers; however, the creeping ischemic necrosis and pain will stop. In order to obtain complete healing of ulcers, femoral-popliteal arterial surgery may be necessary in those patients with superficial femoral artery occlusion on the bad side.

Superficial Femoral Occlusive Disease

Numerous procedures are at present available to increase flow into the popliteal artery. These include autologous vein bypass, endarterectomy with or without venous onlay patch

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and dacron bypass. In the younger patients with claudication and a small segmental lesion of the superficial femoral artery, localized endarterectomy, with or without venous patch, has proved to be highly successful. In more extensive disease, bypassing the superficial femoral artery utilizing a saphenous vein graft has withstood the test of time. Unfortunately, 25% of patients do not have a suitable saphenous vein; therefore one of the other procedures must be utilized.

At the present time all patients with symptomatic aorto-iliac disease should be considered candidates for surgical relief of their symptoms. In femoral popliteal disease it is dependent to a greater extent on the activity of the patient as to whether or not claudication should be treated. The long-term follow-up results, given a well performed delicate surgical technique, are related to the run-off available from the popliteal artery and to the rate of progression of the distal occlusive process. Certainly the two bad actors are diabetes and Buerger's disease. Fifteen per cent of diabetics with claudication will have a segmental occlusive disease amenable to surgical correction; however, these same patients will have fair to inadequate run-off from the popliteal vessels and may therefore suffer from late occlusion. Patients with Buerger's disease usually present with poor run-off and would fall under the same category. As more femoral arteriograms are performed, and with care in the selection of patients, markedly increased success rates are being achieved in femoral popliteal surgery.

Arterial Emboli

The greatest advance in vascular surgery in the last few years has been the advent of the Fogarty catheters as introduced by Thomas Fogarty, University of Oregon Medical School.[15] These catheters enable the surgeon to extract more distal emboli from cutdowns on the common femoral artery, with a very high success rate. The catheters are based on the balloon principle whereby they are threaded down an artery and the balloon blown up as the catheter is extracted. The balloon teases the clot out. These catheters are of great value during vascular surgery when one occasionally encounters distal clotting at the time of proximal arterial occlusion. Formerly, a posterior tibial artery flush technique was used in order to flush a clot out of the tibial arterial tree. Now, one can pass the catheter down the anterior and posterior tibial vessels all the way to the ankle, and extract the clot in a retrograde fashion, with assurance of a patent vessel at the completion of the procedure.

At the present time these catheters are being adapted with a flexible tip for removal of venous thrombi, which should be of considerable technical aid to the vascular surgeon. We have used them in extraction of clots from the caval and iliac venous system; however, in their present state they do damage venous valves and must be used with extreme caution.

Summary

As newer techniques are adopted, some of these concepts will undergo even further change in the near future. It should be remembered, however, that there is no substitute in this field for gentle, careful, expeditious surgical technique. It is hoped that the reader may grasp some of the great strides now being made and continuing to be made in the field.

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4-15 May be secured from the author or the reprints.

Substitutes

It would be too bad if doctors followed the druggists' example and said, "I can't cure what you have, but I can cure something just as good."
— Life

Abstracts, Briefs and Commentaries

VAGOTOMY AND PYLORECTOMY FOR ULCER

The authors state that vagotomy combined with a simple drainage procedure is now an accepted alternative to partial gastrectomy for the surgical treatment of patients with chronic duodenal ulcer. Fears that these operations would be followed by an excessive incidence of recurrent ulcer have been proven groundless. A review of the follow-up of 100 patients with chronic duodenal ulcer treated by vagotomy and gastroenterostomy showed a disproportionate number of patients with post-cibal* symptoms similar to those following a Polya-type resection. Although the incidence appeared to be less than after gastrectomy the authors felt that too many patients still had disturbing symptoms. They therefore concluded that most of these symptoms were the result of anastomosing the stomach to the jejunum; felt that the best operation to combine with vagotomy would be one that maintained normal continuity of the gastrointestinal tract; and attempted to evaluate the operations that would accomplish this: pyloroplasty, pylorectomy, and excision of the anterior half of the pyloric sphincter. The last method, described by Judd and Nagel (1927), was selected as the simplest and safest of the three methods. The authors prefer to call the operation "anterior pylorectomy" because it draws attention to the essential part of the procedure, i.e., the destruction of the pyloric sphincter, allowing the atonic stomach which follows vagotomy to empty its contents more readily. Some patients with vagotomy and gastrojejunostomy, who had post-cibal complaints, were relieved when the gastrojejunostomy was taken down and a portion of the pyloric sphincter removed.

Follow-up on 200 cases so treated now reveals that if vagus nerve division is complete there is no increase in the postoperative occurrence of duodenal ulcer and lessened post-cibal symptoms.

The operation consists of first placing fixation sutures at the upper and lower borders of the pylorus which, when tied, aid to control bleeding. An elliptical incision is then made, removing the anterior half of the pyloric sphincter and taking more of the duodenal wall if there is a tendency to narrowing. The authors' experience is that the remaining lumen is not unduly small, as postoperative emptying is adequate even with a comparatively narrow canal. After excision the opening is closed

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*See Test Your Word Score Page 447.

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transversely by two layers of chromic OO catgut. It is very important to include the mucosa in the sutures, as the mucosa will retract if not included and carefully approximated, or stenosis will eventually follow. The ulcer is not usually removed unless it is included in the excised anterior tissue.

The authors conclude that the operation is a very safe one. There have been only two deaths in 200 cases, one from pulmonary embolism and one from acute enterocolitis. Complications have been few. In their early cases two developed obstruction, probably due to narrowing, the result of retraction of the gastric and duodenal mucosa not well approximated by the sutures.

Ninety-one percent of their operations are classed as satisfactory. The success or failure of the procedure depends very largely on the completeness of the vagal section. The conclusion is that vagotomy and anterior pylorectomy is probably the best operation available for chronic duodenal ulcer.

Stanley R. Maxeiner, Sr., M.D.
Minneapolis, Minnesota

Holt, R. L., and Lythgoe, J. P.: The Treatment of Chronic Duodenal Ulcer by Vagotomy and Anterior Pylorectomy. Brit J Surg 52:1, 1965.

TREATING HERPES ZOSTER

A trial of oral therapy with abitylguanide (ABOB, Smith Kline & French) in 19 herpes zoster patients over a one-year period suggests that if treatment is started early, two or three days after the appearance of vesicles and before severe nerve damage occurs, the lesions usually involute and pain ceases relatively soon. There were no apparent undesirable side effects in any of these patients.

The patients, four male and 15 female, ranged in age from twelve to seventy years; 42 per cent were sixty or older and five were in their twenties. Seven of the patients were seen one to three days after appearance of the vesicular lesions; four were seen four to five days after; six were seen seven days after; and one was seen ten days after. All but two patients complained of pain. Previous episodes of herpes zoster had been experienced by three patients in the same sites as the current one. Two of these had received antibiotics and vaccinations for small pox respectively. These did not help. The other patient had been under treatment for a year for postherpetic neuralgia.

The author presents brief histories of all 19 patients, not reviewed here. From these summaries, it appears that crust formation during ABOB treatment occurred from four to seventeen days after the vesicles first appeared. In those cases in which therapy was initiated within two or three days after the appearance of the vesicles, prior to the occurrence of nerve damage, crusts formed in four to eight days. Eruptions cleared in less than two weeks in nearly two thirds of the cases. More than three weeks were required in only one patient. Of the 17 patients who had complained of pain, 13 reported its disappearance: six within two days; seven within seven to eleven days. Of the four patients with residual pain, all were sixty years old or over. In only one of these had treatment been started early.

Courtesy of Medical Abstract Service
Berwyn, Illinois

Wilkinson, J.: N Carolina Med J 23:357, 1962.

CHANGES IN WESTERN MEDICAL ENVIRONMENT

Although Western medicine has made great advances in recent times, its practitioners receive less gratitude and respect than was common in the past. This disparity between performance and prestige is due to a number of imbalances and difficulties, including increasing reliance on the hospital as the place for diagnosis and treatment, the tendency for medical education to focus on tests and measurements, the fragmentation of patient care into a series of exclusive specialities, the inclination of patients to receive care away from their homes and communities, the bias introduced by private and public prepayment insurance programs that pay for the care of diseases rather than patients, and, finally, the administrative policies of hospitals and clinics, which often determine who is treated and under what circumstances. Teaching hospitals and medical schools often emphasize "aspects of medical service" rather than teaching students how to provide "the care and service patients want and need." In addition, the chronic, academic complaint that patients with trivial or nonexistent illnesses misuse outpatient facilities seems to result from a clinical disinterest in and conceptual unawareness of patients with chronic, undifferentiated dysfunctions. Chronically ill patients with multiple disorders frequently become multiclinic problem-patients who never really receive adequate medical care. Because of their training and the imbalances and difficulties described above, physicians often feel insecure about developing the comprehensive diagnostic and treatment program which many patients require. To remedy this situation, it will be necessary to teach the concept of multicausal etiology, since it operates in many organic and functional illnesses. Additionally, Western medicine must re-evaluate its teaching programs in view of the actual demands made by the patients of the medical generalist.

James Janecek, M.D.
Department of Psychiatry
University of Minnesota

Mering, O., and Earley, W.: Major Changes in the Western Medical Environment. Arch Gen Psychiat 13:195, 1965.

ECTOPIC PREGNANCY

Of 905 ectopic pregnancies treated from 1942 through 1957, 882 were tubal pregnancies, 22 were secondary abdominal pregnancies, and one was an ovarian gestation. The ratio of eccyesis to live births was 1:64, the highest ratio recorded for any large series. Of the multigravid patients, 82% had been infertile for three years or longer before becoming pregnant in the tube. A previous history of pelvic inflammatory disease was found in 56% of the patients. The use of the culdoscope materially reduced diagnostic errors and permitted the treatment of many patients before the diagnosis became obvious, or even before rupture occurred. This helped to reduce the mortality rate to 1.4% in recent years. The free use of blood and antibiotics, as well as a resident staff oriented to expect eccyesis, helped to create a better prognosis for the patient with this condition.

Courtesy of References and Reviews
Journal of the American Medical Association

Bobrow, M., and Bell, H.: Surg Gynec Obstet 20:500, 1962.

INCOMPLETE MASTECTOMY

In some instances surgeons elect to do a simple mastectomy for carcinoma, but in so doing Holleb et al. have pointed out that a so-called simple mastectomy may be merely an incomplete removal of breast substance and nothing more than a removal of the redundant portion of the breast.

This then leaves the individual with either remaining carcinoma cells or remaining breast substance in which carcinoma can again occur.

This again brings up the controversy as to whether or not a simple mastectomy is ever indicated in carcinoma of the breast. In the mind of the reviewer it is not.

Carl O. Rice, M.D.
Minneapolis, Minnesota

Holleb, Arthur I., Montgomery, Robert, and Farrow, Joseph H.: The Hazard of Incomplete Simple Mastectomy. Surg Gynec Obstet 121:819, 1965.

OTITIS EXTERNA

Virtually all manifestations of otitis externa are controllable by the administration of an acid alcohol, or acid alcohol-hydrocortisone, solution. This result, however, is accomplished only after thorough cleaning of the external canal. Cleaning is done painlessly with a proteolytic enzyme ointment as a debriding agent. Therapy is begun only after the external canal is clean. Complete remission of symptoms was obtained in an average of 4.4 days, without any evidence of sensitization to the preparations used.

Courtesy of References and Reviews
Journal of the American Medical Association

Jenkins, B.: Arch Otolaryng 77:442, 1963.

CARCINOMA OF OVARY

In a series of 135 patients with primary ovarium carcinoma, the rate of five-year survival was 21%. Forty-seven per cent died during the first year. The stage of disease at the time of diagnosis was an important factor influencing prognosis. Treatment of most patients consisted of operation and pelvic irradiation. Of 11 recently treated patients, eight who received homogenous irradiation of 3,000 to 4,000 r. to the whole abdomen survived the first year. This new treatment showed promise for short-term palliation. Considering distribution of ovarian cancer among the various ethnic groups in Israel, there seems to be a preponderance among women of occidental origin.

Courtesy of References and Reviews
Journal of the American Medical Association

Ratzkowski, E., and Hochman, A.: Cancer 16:1578, 1963.

SURGERY IN POLYCYTHEMIA VERA

The complications of surgery in 54 patients with polycythemia vera were studied. Postoperative complications occurred in 45% of 62 major operations. Postoperative mortality was 18%. Fifty-two per cent of complications were due to hemorrhage, 18% to thrombosis, and 14% to hemorrhage and thrombosis in the same patient. Complications were four times more frequent in uncontrolled patients than in the controlled group. Patients with short or immediate preoperative control had complicated courses five times more frequently than those with long periods of preoperative control. It is emphasized that caution should be exercised in performing elective surgery in polycythemia. When surgery is indicated, patients should be treated with myelosuppressive agents for as long a period as is required to achieve and maintain a normal blood count or, in the case of emergency procedures, by repeated phlebotomies.

Courtesy of References and Reviews
Journal of the American Medical Association

Wasserman, L.: New Engl J Med 269:1226, 1963.

ECTOPIC PREGNANCY

In 200 consecutive cases of ectopic pregnancy, 95% of the patients complained of pain which was sudden, severe, and unilateral; in 19% it was associated with syncope. A history of vaginal bleeding was obtained in 75%. Ectopic pregnancy was found on the side opposite of the pain in 11 patients. One ectopic pregnancy was implanted at the site of a previous tube ligation. The pregnancy test had limited value both from the standpoint of its accuracy in this condition and the time required to obtain the results. Culdocentesis was performed in 155 patients; the accuracy of this procedure was 97%. On admission, an incorrect diagnosis was made in 53 patients (26%). Abortion, ovarian cyst, acute salpingitis, dysfunctional uterine bleeding, and appendicitis were some of the conditions which were diagnosed erroneously. Use of culdocentesis would have revealed free-flowing blood in 85% of these patients and might have crystallized the diagnosis. In seven patients a positive tap was ignored in determining the immediate management. The past history of a previous ectopic pregnancy markedly increased the possibility of a second extrauterine gestation.

Courtesy of References and Reviews
Journal of the American Medical Association

Chez, R.: Surg Gynec Obstet 117:589, 1963.

ADRENAL STEROIDS IN ULCERATIVE COLITIS

Although adrenal steroids are established as an effective form of therapy of ulcerative colitis, the evidence suggests that they add a definite risk to patients undergoing colectomy. Twenty-one patients with ulcerative colitis given steroids prior to and during colectomy were studied and compared with 18 patients also undergoing colectomy but not receiving steroids. Thirteen complications were found in the steroid-treated group and two in the nontreated patients. Wound infections and small bowel perforations were the most common complications in the steroid group. These perforations deserve special attention. There were five such complications in the steroid group, two occurring through normal intestinal mucosa. None occurred in the nontreated group. The data presented suggest that adrenocortical steroids add a definite risk to patients with ulcerative colitis undergoing colectomy.

Courtesy of References and Reviews
Journal of the American Medical Association

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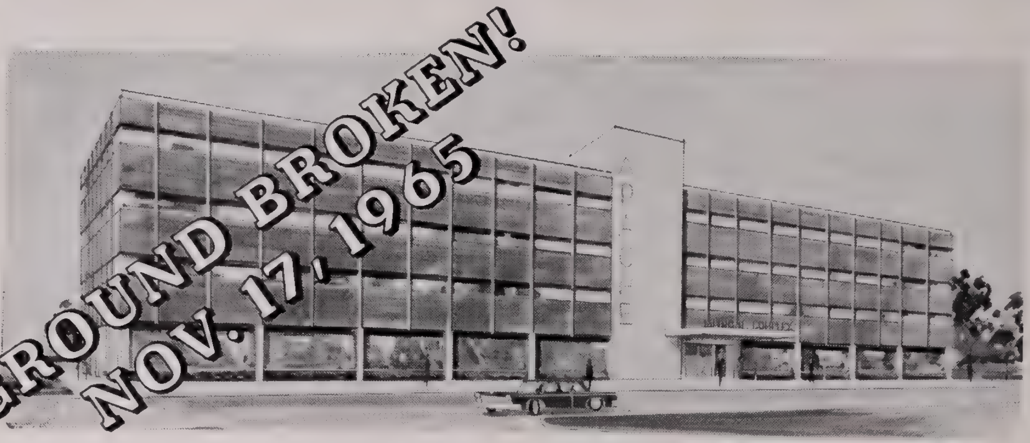
A man should choose with careful eye the thing to be remembered by.
— R. P. T. Coffin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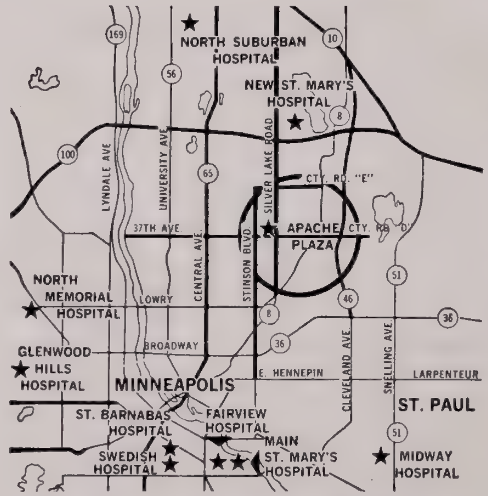
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56
NEW ST. MARY'S HOSPITAL
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Book Reviews

The worst education that teaches self-denial is better than the best that teaches everything else and not that. — J. Sterling

MENTAL RETARDATION: A HANDBOOK FOR THE PRIMARY PHYSICIAN — A Report of the American Medical Association Conference on Mental Retardation, April 9-11, 1964. A.M.A. Publication, 141 pages, price 40¢

This book substantiates the fact that such a conference of 175 persons did occur. As a primer on mental retardation it is inadequate. A careful reader could compile a list of topics about diagnosis, cause, prevention, treatment, counselling worthy of study in authoritative sources. To do this one would overlook the emotionally biased statements which load the text.

In the preface, the editorial committee states that it "undertook to combine and reconcile the reports of the 14 task forces, modifying and supplementing material where necessary and in some cases choosing between divergent views. . . ." Additionally, "We are grateful to Miss Cathy Covert who has served as editor for the proceedings of the conferences. She has participated in an experiment in medical writing with diligence, patience, perseverance, and good humor."

This suggests that the book is not a report of the conference as we are led to believe by the title. Content hews to the line of President Kennedy's Panel on Mental Retardation. Aside from the factual data which should be checked out so that reported items can be seen in proper perspective, the emotional pitch is that primary physicians should be all things to all people. Item by item, criticism would lead to more writing and reading than the report warrants.

Titus Bellville, M.D.
Minneapolis, Minnesota

A HISTORY OF PATHOLOGY — Esmond R. Long, M.D., Dover Publications, New York, $2.00, 188 pages.

With the republication of **A History of Pathology** in soft covers, Dover Publications continues its tradition of resuscitating medical classics. The original 1928 edition is now a collector's item. Dr. Long, still active as the Emeritus Professor of Pathology at the Henry Phipps Institute of the University of Pennsylvania, has penned a new preface and added an appendix on recent trends in Pathology.

The book is well-bound with easily readable print. In contrast to many paperbacks, the photographic plates are unusually clear. The contributions of the great men of medicine are deftly sketched. Dr. Long parades names, events, and dates before the reader without lapsing into a dull recital. When boredom threatens, he relieves the pressure with such nuggets as: ". . . the diarrhea of the short-lived consumptive, Louis XIII, was traced to tuberculous ulcers, among the first to be recorded in the royal bowels."

I was disappointed with the sketchy review of trends in pathology over the last 35 years. But modern medicine does not lend itself to succinct summary, and this does not distract from the book's value. It will prove a valuable source for physicians who seek historical perspective.

Richard L. Reece, M.D.
Minneapolis, Minnesota

THE CHEST FILM IN MASSIVE PULMONARY EMBOLISM — D. J. Torrance, Jr., M.D., Charles C. Thomas, Publishers, 74 pages.

This 73-page monograph of the American Lecture Series is explicit in words and diagrams. The excellent reproductions of the various chest roentgenographs clearly depict the abnormal x-ray findings in pulmonary embolism.

The major contribution by the author is that the "plain film" (x-ray) of the chest is often diagnostic of massive pulmonary embolism. The signs are: a) blanching of peripheral lung field, b) difference in vascular shadows of the two lungs, c) irregularity of the hilar arteries, d) "pruned" hilar artery.

There is often no pulmonary infiltrate and no history of hemoptysis. The major symptom is dyspnea accompanied by hypotension. The electrocardiogram may not demonstrate right axis or heart strain.

I found this a fascinating and easily read book. Every patient is heir to this catastrophe. Every doctor should read this book. Truly, a gem for all!

Jerome T. Grismer, M.D.
Minneapolis, Minnesota

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Gleanings from the Meetings

Western Surgical Association
73rd Annual Session
November 18-20, 1965
Omaha, Nebraska

Problem of Bile Peritonitis* — Thomas H. Wallace, M.D.

Dr. Wallace presented 21 cases of generalized bile peritonitis and gave a review of the results. Seventy-five per cent of these cases followed operation. The cause of bile leakage was distributed between the slipped cystic duct ligature, common bile duct injury at operation, and leakage from common bile duct T tube site. Eleven cases presented a very insidious onset. Nine of these, 45 per cent, were post-surgical. A 55-per cent mortality indicated serious results of bile in the free peritoneal cavity. It was very impressive to note that 100 per cent of the cases which did not receive treatment in terms of correction of the cause had 100-per cent mortality.

A Laboratory Animal Study of Barium Peritonitis**

— Robert H. Westphal, M.D.

Barium sulphate, as used in x-ray studies of the gastrointestinal tract, was injected into the peritoneal cavity of dogs. Following this, various methods of attempting to remove the barium were studied. Hydrogen peroxide was found to be of no particular value as an irrigating substance since it did not remove the barium any better than a saline irrigation. As much barium as could be removed with a saline irrigation was employed, antibiotics were also given, and the author concluded that since barium became rather solidly impregnated in the fatty tissue, particularly that of the great omentum, an omentectomy was of additional aid in removal of the firmly attached barium which would not wash off.

Distal Arterial X-ray Studies in Diabetic Gangrenous States†

— Anthony J. Carnazzo, M.D.

Fifteen diabetic patients had angiographic studies to determine the status of the distal pedal vessels in extremities in which the vessels were compromised or borderline. One method of study involved giving a low spinal to prevent pain, administering a femoral arterial injection, and then making x-ray studies of the vessels of the digits of the foot and of the arterial arches so that an evaluation could be made which would assist in the decision about the level of amputation that could safely be employed. In

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*Bile Peritonitis — A Review of 21 Patients. Thomas H. Wallace, M.D., Charles W. McLaughlin, Jr., M.D.: Univ. of Nebr. Coll. of Med., Omaha, Neb.

**Barium Peritonitis. Robert H. Westphal, M.D. Univ. of Nebr. Coll. of Med., Omaha, Neb.

†Pedal Angiography in Diabetes. Anthony J. Carnazzo, M.D. Dept. of Cardiology, Creighton Univ., Omaha, Neb.

Continued

certain cases minimal toe and foot amputations could be made with reasonable assurance of healing when the x-ray studies indicated adequate arterial supply.

Biliary Diversion as a Means of Correction of Induced Hypercholesterolemia in Animals*

— Harry Keig, M.D.

High serum cholesterol levels were induced in dogs by a prolonged high-fat diet. The common bile duct was transected and an anastomosis made in the terminal ileum at 100, 200, and 300 cm. from the ileocecal valve. Cholesterol levels were found to be reduced in relative proportion to the length of ileal mucous membrane available for absorption of bile and cholesterol. Effective reduction of serum cholesterol was obtained in spite of continuation of the high-fat diet. The author suggests this method as a possible means of managing the problem of hypercholesterolemia.

Investigation of the Portal System Via the Umbilical Vein

— Graham Gallon, M.D.

The authors employed the method of Gonzales and Bailey to cannulate the umbilical vein as an entree to studies of the portal vein dynamics. A 5-cm. incision was made in the skin of the midline halfway between the umbilicus and zyphoid. (The umbilical vein is found in the preperitoneal fat under the transversalis fascia.) Fifty cc. of 50-per cent Hypaque was injected, and 10 serial exposures were made in 10 seconds and another at 15 seconds. In 95 per cent of patients with suspected portal hypertension the umbilical vein was found to be patent. The authors had used a polyethylene catheter left in place for two weeks while various chemical studies were done. They have not suggested this method as a replacement for splenal portography but as an additional means of safe and direct study. They obtained a visualization of the portal vein, main trunk, superior mesentery, coronary, gastroepiploic and collaterals to the portal and splenic veins. Only two contraindications to this study were cited, those of allergy to Hypaque and of renal insufficiency. Allergic reaction was excluded by a 1-cc. intravenous injection 24 hours prior to the study.

Hematomas Within the Wall of the Duodenum**

— Robert J. Freark, M.D.

Eight patients collected within a five-year period were reported. Blunt trauma was the most common cause of such hematomas. Contrast studies were usually necessary to confirm the diagnosis, after routine survey films had suggested the possibility, following the observation of a dilated stomach and possibly an obliterated rectus muscle. Blood escapes into the submucosal or subserosal space of the duodenum, and symptoms and physical findings may simulate acute appendicitis, a ruptured viscus, an abdominal tumor, or high small bowel obstruction: the history of trauma being of the essence. The average time between injury and establishment of diagnosis is 12.8 days. Contrast studies revealed the picket fence or coil spring sign and occasionally a mere trickle of barium passing through the obstructed duodenum. Simple evacuation of the hematoma was adequate surgical management in two of the cases, and in the remainder a gastroenterostomy was also added.

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*Correction of Hypercholesterolemia by Biliary Diversion. Harry Keig, M.D. Creighton University, Omaha, Neb.

**Intramural Hematomas of the Duodenum. Robert J. Freark, M.D., Chicago, Richard D. Corley, M.D., Chicago, William T. Norcross, M.D., Chicago, Lee Strohl, M.D., Chicago.

In the discussion Dr. Mathewson of San Francisco cited four cases, all of which required only evacuation of the hematoma for recovery. Dr. Soper of Iowa City suggested that one should be alert to this problem in the battered child syndrome.

The Redistribution of Blood After Relief of Obstructed Common Iliac Artery* — Samuel L. Kountz, M.D.

In cases of impending gangrene of one extremity an endarterectomy or bypass graft of one obstructed common iliac artery is performed. This may result in return of viability to the involved extremity, but in turn, blood is "stolen" from the aorta, its branches and in particular the opposite iliac artery, causing the leg to become ischemic. Definitive reconstructive surgery on this iliac artery restores circulation to this extremity but, in turn, "steals" blood from the mesenteric circulation, resulting in classical intestinal angina. If such a steal persists, gangrene of the intestine with death may ensue. Experiments were performed on dogs to demonstrate the shifting of blood from vascular beds in which there was more resistance to those with lesser resistance. These studies consisted of partial constriction of the superior mesenteric artery designed to simulate clinical cases. Release of the partial obstruction did not bring a full return to normal flow. However, periarterial sympathetic neurectomy did achieve a return to normal flow; and the author therefore suggested that this procedure might be of value in emergency situations in which there is massive infarction.

In clinical cases the diagnosis was proven by mesenteric and celiac arteriograms. The intestinal ischemia symptoms were relieved by nasogastric suction and abstinence from food. This therapeutic trial aided in the clinical diagnosis of mesenteric ischemia.

In the discussion, Dr. Fry of Ann Arbor, Michigan, cited 12 cases of visceral arterial insufficiency. He stated that all distal iliac insufficiencies should have an aortogram and that both iliac arteries should be studied prior to corrective treatment of the symptomatic extremity.

Popliteal Aneurysm** — Masuki Hara, M.D.

This report concerns a group of 20 patients with 29 popliteal aneurysms, 13 of whom suffered acute vascular insufficiency of the leg. Eight of these required supracondylar amputation of the involved leg, and one had a bilateral amputation. All but one were previously asymptomatic, although two were aware of a mass in the popliteal fossa. Two patients with acute thrombosis still exhibit severe ischemia of the viable extremity despite emergency operation. The results of elective aneurysmectomy and grafting were gratifying, with only one failure out of seven procedures. Three patients had been misdiagnosed and admitted to the orthopedic service; two were explored with a diagnosis of fibrosarcoma and Baker's cyst,

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*Aorto-iliac "Steal" Syndrome. Samuel L. Kountz, Palo Alto, Donald R. Laub, Palo Alto, John E. Connolly, Palo Alto.

**The Hazard of the Popliteal Aneurysm. Masuki Hara, M.D., Little Rock, Arkansas, Bernard Thompson, M.D., Little Rock, Arkansas.

Continued

respectively. The author concludes that the untreated popliteal aneurysm is fraught with constant danger of an acute or chronic occlusion, and that aneurysmectomy with grafting prior to such a catastrophic episode is the recommended procedure.

Study of Changes in DNA Synthesis As An Evaluation of Tumor Cytotoxic Agents*

— Gerald O. McDonald, M. D.

Since a major problem remaining in cancer chemotherapy is the difficulty of determining which drug will produce the maximal cytotoxic effect in the tumor of an individual patient, the authors developed a method of evaluating this effect by observations of changes in DNA synthesis. The in-vivo effect of two groups of drugs on DNA synthesis was evaluated in Ehrlich ascites carcinoma maintained in CF-1 mice, the effects being observed at multiple timed intervals from one to 96 hours. The results showed excellent correlation between carcinostatic or noncarcinostatic activity of the previously determined drugs, which were then compared in quantitative fashion with changes in DNA synthesis in the cell population. The DNA molecule was appropriately tagged for observation by employment of radioactive thiamin. In clinical patients an incision biopsy was obtained from the tumor and a cell culture was exposed to radioactive thiamin. The patient was then given the cytotoxic drug, and a repeat biopsy was made with a similar comparison and subsequent evaluation of the cell activity of the tumor by measurement of the radioactive thiamin uptake as an index of the DNA synthesis. In some patients in whom the percentage of uptake increased following cytotoxic drug administration, the tumor actually accelerated.

This method of utilizing changes in DNA synthesis as a screening procedure for candidate carcinostatic drugs is suggested as a method to determine the most effective agent, and in some situations to ascertain whether a cytotoxic agent may in fact accelerate the tumor growth.

Operations Upon the Vena Cava in Prevention of Pulmonary Embolism**

— John J. Bergan, M.D.

Three vena cava operation procedures were studied over the past seven years on 34 patients. All but two of these patients had sustained recurrent pulmonary embolus while under adequate anticoagulant therapy, or were unsuitable for this type of medication. In 11 patients with a vena cava ligation, one died of proximal cava thrombosis, seven with varying degrees of edema. Four patients with postoperative edema had cutaneous ulcers due to severe venous stasis, but none was incapacitated. In 11 patients with a vena cava plication of the Spencer type, one died during surgery, four have some degree of ankle edema, and six are asymptomatic. Cavagram showed an occluded cava in six of nine patients studied, and recanalization was not seen for as late as two years following surgery. Twelve patients had a DeWeese type of vena cava filter operation wherein a grid or screen of sutures was placed across the vena cava. In 11 patients studied by cavagram all were patent; four had varying degrees of ankle edema, and eight were asymptomatic.

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*Quantitative Changes in DNA Synthesis As an Indicator of Tumor Cytotoxicity. Gerald O. McDonald, M.D., Chicago, James N. McIver, M.D., Chicago, Augusto J. Llamas, M.D., Chicago, Howard H. Sky-peck, M.D., Chicago.

**Critical Comparison of Vena Cava Ligation, Plication and Filter Operation in Prevention of Pulmonary Embolism. John J. Bergan, Chicago, David W. Kinnaird, Chicago, Karl Koons, Chicago, Otto H. Trippel, Chicago.

None of the patients having either ligation, plication, or filter operation sustained a postoperative pulmonary embolism. Each of these procedures, therefore, achieved its objective of eliminating recurrent pulmonary emboli. The 15 patients with proven cava patency have had less recurrent phlebitis, edema, and stasis stigmata than the 17 patients with occluded cavae. Several of the patients, however, did have chest pain suggestive of the possibility of small pulmonary emboli in the immediate postoperative period.

The authors performed their vena cava procedures by retroperitoneal approach. However, in the discussion, Dr. DeWeese (Columbia, Missouri) prefers transperitoneal approach by a long midline incision to facilitate the more precise approach to the vena cava for that particular technique of manufacturing a suture screen, and also to permit ligation of both ovarian veins. He cites one case of death which he believed due to embolization from ovarian vein.

Dr. Moretz (Augusta) suggests the value of placing the screen or plication conveniently below the large vein, preferably a lumbar, to permit inflow directly proximal to the screen.

Management of Ligation of the Hepatic Artery*

— William M. Monafo, M.D.

This paper reports a group of 11 adults in whom the continuity of the hepatic artery was accidentally interrupted. This occurred during cholecystectomy or pancreatico-duodenal resection in four instances and once during gastrectomy, nephrectomy, and resection of hepatic artery aneurysm, respectively. There were two cases associated with operative injuries to the common bile duct. The proper hepatic artery was ligated in six, the common hepatic in three, the right in one, and the left in one. Reconstruction of the artery was performed four times — with one death. None of the seven patients in whom reconstruction was not performed survived. Hepatic infarcts were found at necropsy in all seven cases. Detailed postoperative study of hepatic function was performed in four instances. These data indicate that when death does not occur, sufficient derangement of hepatic function follows ligation of the common or proper hepatic artery even when reconstruction is performed and there may be minimal clinical illness. The serum glutamic oxaltransaminase and alkaline phosphatase are elevated. In two cases of death on the fourth day after injury, the serum glutamic oxaltransaminase rose to more than 1250 units the day before death. The author points out that the absence of liver cyanosis at the time of injury is an unreliable sign of absence of damage.

In the discussion, Dr. Jacob Berman of Indianapolis states that even in the cirrhotic patient with good collateral venous circulation, the patient cannot survive ligation of the vessel close to the liver. He further relates dog experimentation in which, even though the animals were prepared with antibiotics, all died of liver necrosis when the hepatic artery was ligated near the liver. If, however, the hepatic artery is ligated proximal to the gastroduodenal artery or near the celiac axis, all will survive.

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*Accidental Ligation of Hepatic Artery. William W. Monafo, M.D., St. Louis, Jesse L. Turnberg, M.D., St. Louis, Richard Kempson, M.D., St. Louis, Harvey R. Butcher, Jr., M.D., St. Louis.

Continued

Changes of Liver Function Associated with Acute Pancreatitis*

— Marion C. Anderson, M.D.

Acute experimental pancreatitis of varying severity was produced in dogs, and chemical determinations of various features of liver function were performed. This study revealed that with increasingly severe pancreatitis, hepatic sinusoids become distended with blood and there is marked congestion of veins and lymphatics in the periportal spaces. Hepatic function tests became progressively more abnormal as the degree of pancreatitis increased. Only two animals had elevated serum bilirubin, but all revealed other aberrations of liver function. The authors' conclusion on their experimental findings indicates that liver damage associated with pancreatitis begins with intrahepatic circulatory congestion, which may progress to hepatocellular necrosis. Depression of liver function may explain the development of jaundice in some cases of pancreatitis, as well as the toxicity which accompanies severe forms of this disease.

Transhepatic Cholangiographic Studies**

— Fred R. Plecha, M.D.

Twenty patients were evaluated by means of percutaneous transhepatic cholangiography. Seventeen were jaundiced. The extrahepatic biliary tree was visualized in 15 of the 17, and in only one of three nonjaundiced patients. X-rays clearly differentiated between hepatocellular or intrahepatic and extrahepatic obstructive jaundice. The site of obstruction was well localized. Three of these patients were spared an exploratory laparotomy because of the findings at P.T.C. The authors state that there is no practical use of the test or procedure if the jaundice has subsided over three weeks previously.

In the discussion, Dr. Large (Detroit) states that this procedure is most useful as an aid to differentiate between carcinoma of the pancreas and chronic pancreatitis. The sharply cut-off obstruction of the distal duct in carcinoma is opposed to the tapering obstruction in pancreatitis.

Dr. Hanlon (St. Louis) states that on percutaneous cholangiography several patients revealed bile leaks, some requiring laparotomy. A 1-cm. slit was observed in the parenchyma and surface in some instances. Since these observations Dr. Hanlon now employs a Rochester needle so that a polyethylene tube can be left in the liver for a period of drainage. Dr. Mathewson of San Francisco suggests the importance of aspiration after the x-ray, so that the ducts may be decompressed. He feels that his method will avoid the leakage problem.

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*Alterations of Hepatic Morphology and Function Associated with Acute Pancreatitis. Marion C. Anderson, M.D., Chicago, John M. Beal, M.D., Chicago.

**Percutaneous Transhepatic Cholangiography. Fred R. Plecha, Capt. USAFMC, San Francisco, Robert N. Grant, Capt. USAFMC, San Francisco, Carl W. Hughes, Col. USAFMC, San Francisco, Carleton Mathewson, Jr., San Francisco.

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Alcohol is something which very often puts the wreck in recreation.

The Johnson Way

Special Article

Hostility and Disease

ALAN CHALLMAN, M.D.[*]
Minneapolis, Minnesota

THE IDEA THAT hostility is a factor in the production or aggravation of disease is certainly not new. Almost two hundred years ago John Hunter made his well known statement that his life was at the mercy of any street urchin who angered him. He is said to have died a coronary death in a fit of rage.

Derivation

The word "hostility" derives from a root that originally meant "stranger". From time immemorial the paramount question upon sighting a stranger has been "Is he friend or foe?" Over most of human history this question was far from academic—one's life might well depend on the answer. Our own uneasiness in attending a social gathering may represent the vestigial remains of this formerly vital concern; but now, since strangers we meet at parties seldom do us any bodily harm, we can take a drink or two and tranquilize the ancient anxiety.

The "friend-or-foe" alternative led the root word "host" to develop in two opposite directions—"host" meaning one who cares for or entertains strangers, and "host" also meaning "army" that "takes care" of strangers in battle. In current English we have the words "hostile", meaning unfriendly and malevolent, and the word "hostel", meaning a place providing lodging and meals for traveling strangers. We find the related words "hospital", "hospitable", "hostess", "hospitality", and "hotel" bespeaking a friendly attitude toward a friendly stranger or outsider; and another group, "hostile", "hostility", and "hostage" referring to unfriendly relationships.

To me it seems but a little step from this primordial concern about the stranger to our ever-present and seemingly basic fear and hatred of difference. Strangers are people from a different region, tribe, or village. We have developed a constitutional dislike of differences. People who disagree with our ideas we find disagreeable; people of a different religion or skin color, of different national origin, of different politics or economics; even those persons whose "subversive treachery" conflicts with our national purposes we find reason to fear and hate.

Definition

The ambiguity we sense in the etymology of the word "hostility" appears whenever we attempt to assign an exact meaning to it. Like metallic mercury it looks like one piece but fragments when we try to handle it. Sometimes hostility means simply the emotion anger; sometimes it means a personal trait of character—the proneness to take offense, feel resentment, and seek vengeance.

Since we cannot capture this term in precise definition nor get it in pure culture for analysis, we must pursue it wherever it is found in order to learn of its *uses* rather

Continued

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[*] Delivered at Annual Symposium, Mt. Sinai Hospital, of L. E. Phillips Psychobiological Dept. on February 29, 1965.

than of its *essence*. Imprecise terms of this sort should never be wholly condemned since they can be of great value: they permit us to agree when we choose, or to disagree if we prefer; and their very vagueness permits us to explain anything we wish with them. Words can be rich or poor. The word "pi" is a poor word since it means only 3.14159+ and nothing else. The word "love" is a rich word.

Hostility is another rich word, and if we aren't careful we may find we have another "explain-all" term. To be as specific as possible, hostility can be defined as an emotion associated with attacking or destroying. An emotion is a feeling that tends to move out.

Complication

When hostility is conscious, it is perceived as some degree of anger; but it often operates outside of consciousness so that the subject is aware of the attack, but not of feeling angry. To the extent that this happens, we cannot rely upon the most conscientious reporting of a subject as to whether he is hostile or not; his denial may be actually untrue; hostility so frequently occurs in a mixture of emotions. Aside from the ambivalence regularly found in love and hate, which is tangential to my concern here, a confusing mixture of hostility and fear is more often encountered than a pure culture of either.

Evocation

Anger and fear are reactions to a threat. When the threat appears overwhelming or unmanageable, fear is experienced; when the threat appears manageable it evokes anger; and when the force and counter-force are fairly matched, a mixture of anger and fear occurs. War heroes report feeling afraid while they attack and destroy. The same situation with a slight shift in power may evoke fear now and anger at another time, as when a small boy encounters a known bully — either alone or when accompanied by his big brother. We also see instantaneous shifts from anxiety to anger in a husband's reaction to the onset of an illness in his wife, possibly because irritation is more comfortable than worry.

A threat characteristically elicits objective defense and subjective responses of fear or anger. Broad highways of interchange connect the threat-defense-attack triangle. Self-preservation operates largely around this triangle: i.e., the perception of a threat, the preparatory arousal and strengthening for the appropriate response of defense or attack, and the carrying out of the action.

As long as one visualizes only threats that are external and obvious, the evocation of hostility or fear follows lines of common-sense reasoning. As soon as one leaves this well-lit, orderly, text-book-type world for the world of actual affairs, one finds anxiety or hostility with no obvious antecedent. For the explication* of that hostility which has no obvious origin, we prefer a model which is more sophisticated though still related to the threat-defense-attack paradigm. In such cases we may say with Freud that hostility is evoked by the frustration of a need.

Identification

Sometimes it is easy to recognize and identify hostility in a human encounter or relationship, as in the case of a punch in the nose; but sometimes it is impossible, as in the case of a charitable donation intended to deprive a legitimate heir of part of his inheritance. In most instances, the idea that hostility is involved must be at best a conclusion or at worst an inference.

Objective Signs

Objective signs of hostility are often abundant, since muscles are deeply involved in (e)motional expressions. Facial expression, posture, gestures, pitch and volume of voice, tremors, actions, respiration rate and volume, heart rate and volume are objective indicators of hostility. It will be a great advance when laboratory instruments can measure, assemble, and identify these data; but for the present the human brain can outdo any scientific apparatus in speed and accuracy and must be our main reliance in identifying hostility. Fortunately the human brain is the only computer-like mechanism that can be mass produced by unskilled labor.

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*See Test Your Word Score Page 447.

Since there is an inevitable relationship between subjective emotion and objective somatic effects, it is difficult to see how any person can question the occurrence of "physical symptoms" in emotional states unless he is prejudiced against such a conclusion.

Subjective Signs

Subjective aspects of hostility are scrutinized by an even more refined internal identification system than are objective signs. As a rule emotions are not initially recognized as emotions but rather as appropriate and inevitable attributes of the situation. They first appear in consciousness as perceptions of external events rather than as personal reactions to them. The first step is a surge of unidentified feeling, seemingly related to the event; then identification of the feeling may occur, or it may be obscured or bypassed completely. At this latter stage, the inevitability of the reaction and the predominant role of the event are implied in the commonly heard "He *made* me angry" (very uncommon is "I got angry at him"). Finally the opportunity arrives for a more or less detached consideration of the propriety of the reaction, and the advisability of displaying it or acting upon it.

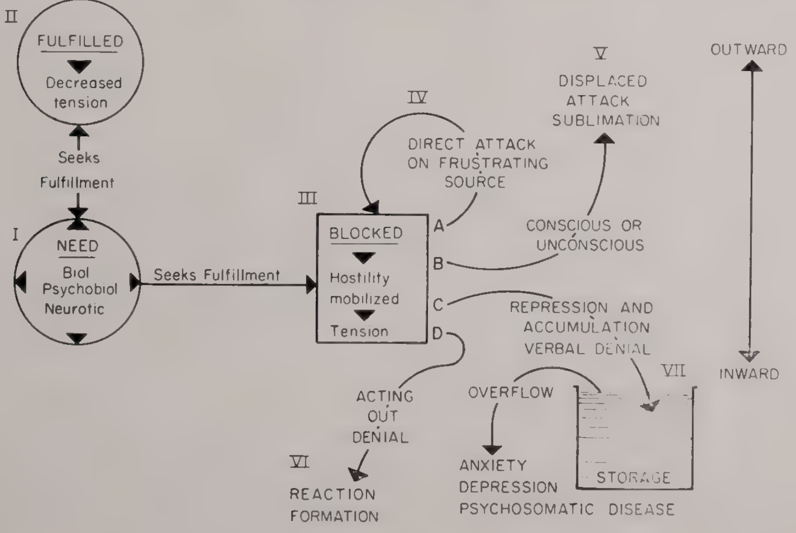
Suppression

In addition to the period of anonymity of the emotion, the content of the feeling may be found on review to be reprehensible, as would a sexual feeling for a close relative; or provocative of an undesirable retaliation, as would a feeling that the boss is dishonest. In either case the feeling would be suppressed, i.e., intentionally pushed out of consciousness. Following repeated acts of suppression the process becomes automatic, as conscious intention is no longer needed when repression occurs. Both suppression and repression interfere with the subject's capacity or willingness to report his emotion to another person no matter how ready the other is to accept and forgive.

Succession

An additional confusing factor in reporting or recognizing emotion is the commonsense practice of considering the subjective feeling and objective behavior in a cause and effect sequence to each other, rather than as simultaneous manifestations of a preceding cause. Characteristically we say, "He pointed his gun at me and my heart began to pound." In such a case it would be easy to elicit the additional information that the reporting person was also afraid of being shot and not afraid of the pounding heart. In cases where no gun is pointed, and the trigger for the emotional reaction is obscure, we usually hear, "My heart began to pound and I thought I was having a heart attack." If the accompanying fear is admitted, it will

SCHEMA FOR ORIGIN AND DISCHARGE OF HOSTILITY


II
FULFILLED
Decreased tension
Seeks Fulfillment
I
NEED
Biol
Psychobiol
Neurotic
Seeks Fulfillment
III
BLOCKED
Hostility mobilized
Tension
A
B
C
D
IV
DIRECT ATTACK ON FRUSTRATING SOURCE
V
DISPLACED ATTACK
SUBLIMATION
CONSCIOUS OR UNCONSCIOUS
REPRESSION AND ACCUMULATION
VERBAL DENIAL
VII
STORAGE
OVERFLOW
ANXIETY
DEPRESSION
PSYCHOSOMATIC DISEASE
ACTING OUT
DENIAL
VI
REACTION FORMATION
OUTWARD
INWARD

Continued

usually be reported as subsequent to and caused by the heart action. Here the subjective feeling is reported as caused by the objective manifestation. However, we generally hear the reverse, as when we say, "I cried because I was sad", or "I trembled because I was afraid". This common-sense point of view makes for untold difficulties in medical practice. It not only influences the patient's reporting, but also affects the physician's understanding, as in the mind-body controversy, and in seeing the unity in psychosomatic disease.

Intention

Once hostility is aroused by the frustration of a need it seems that it must find a mark to strike. Normally it strikes outward against the person, object, or situation considered responsible for blocking the fulfillment of the need. In unmodified form as we see it in a small child, it is expressed as a blow, a bite, or a push. The schema illustrates the interplay of these forces and reactions.

Modification

Such primitive action is impractical for adults under most circumstances; therefore the expression is modified and may come out as a verbal tirade that "breaks no bones." This, too, may be inappropriate if the offending party or spectators are deemed to have such power, or be in communication with such persons, as could make a tirade dangerous. The hostility is then suppressed or repressed. Such operations merely retain the feeling and result in increased tension until it is discharged.

Displaced Hostility

The hostility must still find a mark to strike. It may be "*displaced*" to strike outward at a substitute object other than the one blocking the fulfillment of the need, as in the man scolding his children for very little after a "hard day at the office." Likewise, survivors of concentration camps reported feeling little hostility toward camp officials, but were enraged at fellow inmates chosen to transmit and supervise official orders.

Sublimated Hostility

The withheld hostility may also be "*sublimated*" by engaging in sports, games, vigorous exercise and the like. Both displacement and sublimation permit a socially acceptable outward expression of the hostile feelings, and generally these mechanisms along with the direct attacks suffice to discharge the hostile tension. If the hostility is considered especially reprehensible, however, as when it is more or less continuously directed toward one's own small child, it may be denied in consciousness and the denial reinforced by "reaction formation", which consists in "spoiling" the child with indulgence, material gifts, and restrictions. These actions, though rationalized as being for the child's welfare, adequately express the hostility in disguised but crippling form.

Distortion

Not infrequently, an individual's style of life does not permit an adequate "acting out" of hostility; consequently a gradual accumulation of tension may occur, especially in individuals with inherently fiery dispositions and in those who live under exceptionally frustrating conditions.

Castigation

As undischarged hostility accumulates within the person, the mark it finds to strike at is also within the person. This is first evidenced as sharp self-criticism and may go on to produce a firmly fixed conviction of inferiority and guilt, tantamount to a continuing self-attack. In such cases the attacker is generally anonymous, and the source is attributed to the afflicted individual's "recognition of the very truth", or to his projection of "what they think".

The most dramatic and pronounced cases of internally directed hostility occur only after many years of following a containment policy and are called "anxiety reactions" and "depressions". In these conditions the patient sees himself, and is usually seen by others, as the sufferer and victim, rather than as the perpetrator. The attacking force is again not identified; yet whose is the threatening, punishing, accusing voice if it isn't the person's own? Who says, "You're dying" or "You're going crazy" to the anxiety case, or "You're no good and never were any good" to the depressed? Hostility has found its mark. Since it wasn't permitted expression it has turned inward. The fact that the victim of anxiety or neurotic depression is also the one who has been blocking the expression of the hostility implies a type of poetic justice, I suppose, in determining the direction the hostility finally takes. There must be a very large reservoir in the human breast to contain the withheld hostility, since anxiety attacks and neurotic depressions usually don't appear until the fourth decade of life, even though the policy of containment has been followed since late adolescence in most cases. This delay in the outbreak of symptoms could well be the longest incubation period found in disease. It has made for great difficulty and uncertainty in grasping the genesis of anxiety and neurotic depression.

Somatization

When suppression and repression of hostility have been used too much over too long a time, the human storage facilities appear to overflow at some point. In anxiety reaction and neurotic depression the symptomatology of the overflow remains largely in the psyche, and the soma in such cases is found remarkably free of disease. The anxiety and depression apparently serve to channel the discharge of the reservoir overflow without damage to the existing structures in the body machinery. When these painful but relatively safe channels are not opened, the energy flows outward through a bodily organ or organ system, disorganizing it functionally and structurally. A good deal of thought has gone into discovering how the choice of the particular organ is made or whether it volunteers for service. The concept of psychosomatic disease, although it is a thorny issue that requires careful handling, probably does represent a needed, though crudely shaped, bridge across the stream separating psyche from soma in our twentieth-century minds.

Reduction

One advantage in any theory of the genesis and evolution of disease is that it permits a rational approach in coping with the problem; but since it is only a theory, all irrational approaches remain available. In terms of the above theories about hostility one may set about reducing its force or its consequences by: (1) encouraging direct expression through word symbols instead of blows, and with sufficient frequency so that the hostility is expended in "nickels and dimes" instead of in dollars; (2) encouraging displacement and especially sublimations as indirect expressions; (3) encouraging the recognition *and* naming of the emotion in the sentence form "I am angry", rather than "she makes me angry". This operation both detaches the feeling a little from the situation, thereby increasing responsibility and the possibility of control, and invokes the "Rumpelstiltskin phenomenon" which magically reduces the power of a thing by finding its proper name.

Prevention

Hostility may be prevented to some extent if the specific need which is being blocked is discovered and somehow more nearly fulfilled. The simplest prototype of this operation is to remove the steely fingers from the throat of a suffocating person. If the situation is more complex, as it usually is, the preventive measures will be directed toward better fulfillment of all needs—the building up of life's satisfactions in every way possible. In neurotic patients this usually means attempting to improve performance by lowering personal standards. This is a slow, uncertain route to take and generally leads to the therapist being considered an advocate of the devil.

On the other hand, it is enhancing to the professional man's reputation in most circles if he encourages religious faith and prayer in those who seek to control everything, as do hypochondriacs, for instance. Prayer appeals through language to the supernatural force for assistance, as does worry, through the pagan rites of suffering and sacrifice. However, prayer is more comfortable and more easily discontinued when it becomes excessive.

Summation

Hostility is attacking and destroying. It is closely related to fear and to survival and cannot be completely eliminated. It is evoked

Continued

by the blockage of a need. Once evoked it must find a mark to strike. It will strike *outward,* directly at the source of frustration; be displaced upon a substitute person or object in more or less disguised fashion; or be expressed in reaction formation, which is overtly a denial, but covertly a fulfillment of the hostile intention. If long prevented from outward expression by being suppressed and repressed, it may finally strike *inward* at the person concerned, who thereupon assumes the role of hapless victim. In this case the wounds produced are known as anxiety reaction, depression, and psychosomatic disease. If any or all of this is true, a rational way to cope with these problems is proposed.

Rumpelstilzchen*

There was once upon a time a miller who was poor, but he had a beautiful daughter. He told the king he had a daughter who could spin straw into gold. The king was skeptical but told the poor miller that if his daughter could spin straw into gold he would put her in a room full of straw, and if she did not spin the straw into gold by morning she must die.

As the beautiful daughter sat in the room weeping and worrying, knowing that she could not fulfill her father's promises, a small dwarf appeared before her and asked her what she would give him if he would fulfill the promise. She offered her necklace and he spun the straw into gold.

When the king observed this he was surprised and delighted, but he was skeptical. He therefore decided that it would be necessary for her to spin straw into gold once more.

The second night the small dwarf repeated the favor when the girl offered him her gold ring. The third night she had nothing more to offer, but the dwarf extracted the promise from her that he could have her first child after she married the king, who had promised to do so if she could again spin the straw into gold.

A year later, after the child was born, the dwarf returned and demanded his reward. The king pleaded and offered numerous alternatives; but because the dwarf wanted only a live child he refused to accept anything else. Finally, however, he agreed that if the beautiful queen could identify him by his name she could keep the child.

All manner of names were suggested and a commission was appointed to search out various names, but always his answer was "No." She was allowed three days and on the third day the messenger returned stating that he had discovered no new name, but that as he was walking high in the mountain in the corner of the woods, where the fox and the hare say goodnight, he discovered a small house and before the house there was a bonfire. Around it danced a laughing small man, singing and rejoicing:

Heute back' ich, morgen brau' ich,
Ubermorgen hol' ich der Konigin ihr Kind;
Ach, wie gut ist, dass niemand weiss,
Dass ich Rumpelstilzchen heiss'!

When the queen, the next day, pronounced his name the dwarf became enraged and declared that the devil had told her. He screamed and stamped his right foot so angrily that it sank deep into the earth, where it stuck. In a fit of rage he seized his left foot with his hands and tore himself in two.

This is the Editor's free translation from the original German story. — Grimms Märchen

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*See page 523.

Grimm Kinder-Marchen phienemanns Verlag Stuttgart.

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(See overleaf)

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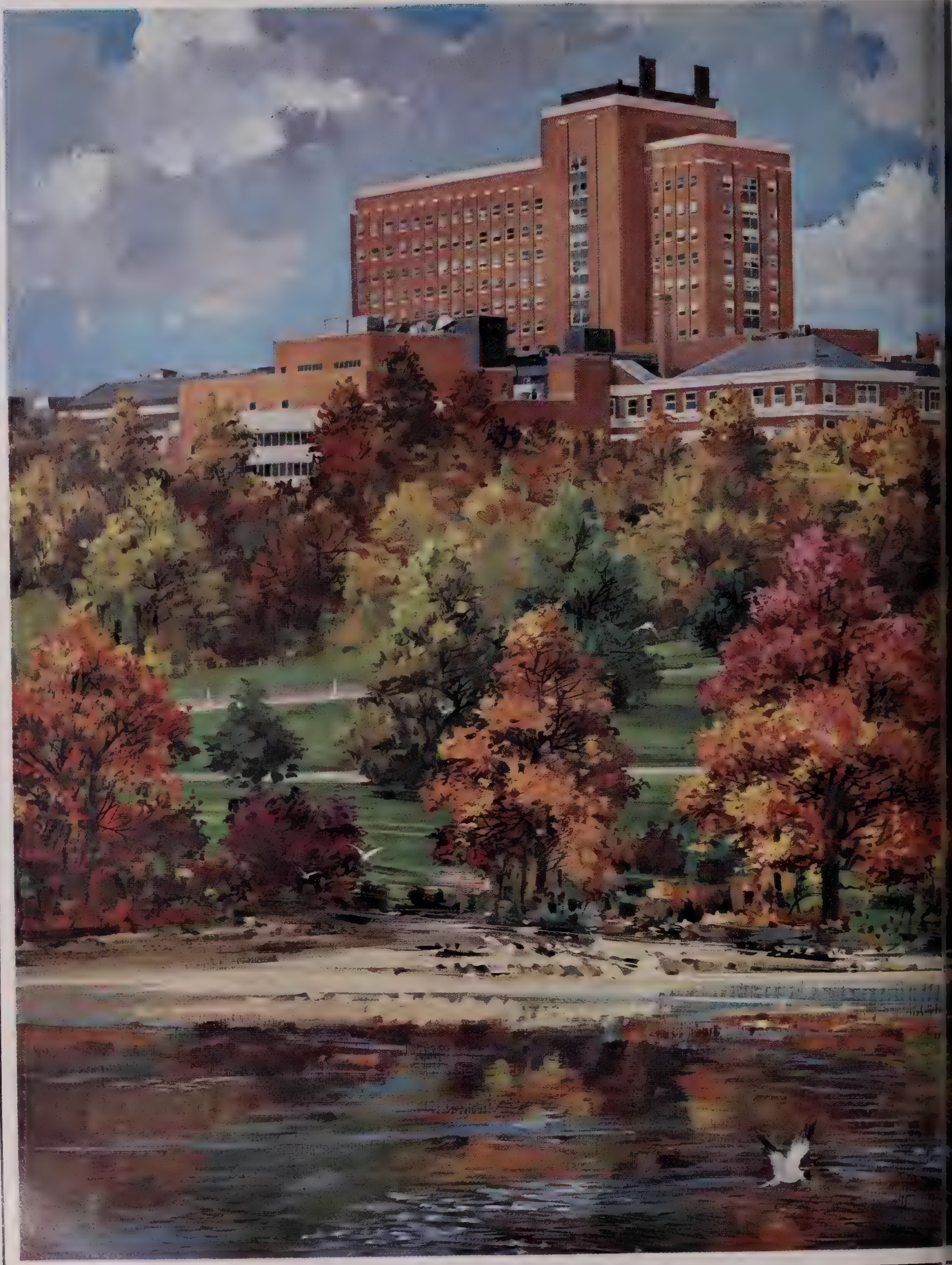

The impressive complex of buildings comprising the University of Minnesota Medical School is reproduced here from an original painting by John C. Berkey. The painting was commissioned by E. R. Squibb & Sons as part of the Collegia Medica program, and presented to the University of Minnesota Medical School in March, 1966. Full color reproductions suitable for framing are being sent to each graduate and made available to each student of the school.

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Contraindications: Allergic or idiosyncratic reactions to carisoprodol.

Precautions: 'Soma', like other central nervous system depressants, should be used with caution in patients with known propensity for taking excessive quantities of drugs and in patients with known sensitivity to compounds of similar chemical structure, e.g., meprobamate.

Side Effects: The only side effect reported with any frequency is sleepiness, usually on higher than recommended doses. An occasional patient may not tolerate carisoprodol because of an individual reaction, such as a sensation of weakness. Other rarely observed reactions have included dizziness, ataxia, tremor, agitation, irritability, headache, increase in eosinophil count, flushing of face, and gastrointestinal symptoms.

One instance each of pancytopenia and leukopenia, occurring when carisoprodol was administered with other drugs, has been reported, as has an instance of fixed drug eruption with carisoprodol and subsequent cross reaction to meprobamate. Rare allergic reactions, usually mild, have included one case each of anaphylactoid reaction with mild shock and angioneurotic edema with respiratory difficulty, both reversed with appropriate therapy. In cases of allergic or hypersensitivity reactions, carisoprodol should be discontinued and appropriate therapy initiated. Suicidal attempts may produce coma and/or mild shock and respiratory depression.

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History of Medicine

Rudolf Ludwig Karl Virchow

(1821-1902)
"Omnis Cellula E Cellula"

Part II*

Invited to Wurzburg to assume the chair of pathological anatomy, he spent seven productive years there. Lecturing and demonstrating at his specially made desk in the Wurzburg Krankenhaus, the tiny, fiery professor used microscopes to convince students that cells reproduced from other cells, and taught that disease results from disturbance of cells by injury or irritants.

Due to his accomplishment in Wurzburg, he was invited to return to Berlin to become Professor Ordinarius of Pathology. Virchow accepted with the proviso that the government build him a new pathologic institute. Soon after assuming this position, he published his greatest work. Die CELLULARPATHOLOGIE fixed the minds of medical men on the consideration of diseases almost exclusively as an anatomical disorder of organs and cells. "He proceeded to rebuild pathology on his true conception of the human body as an organized cell state, a social system of continuous development, in which each microscopic unit performed its part. All fields of pathology were cleared by the new knowledge. Inflammation, tumor growth, degenerations, etc., were to be thought of now in their cellular relations, and in each of these fields Virchow himself led the way in bringing about the change. . . We are all cellular pathologists today, taking our post-Virchovian cellular sense for granted."[5]

His second love, politics, claimed attention and in 1861 he became a member of the municipal council. He also devoted much time during this period to army sanitation. He was nearly sixty when he entered the Reichstag in 1880. "The number of his public activities was almost beyond belief, most of them, including those in the Berlin city council and parliament, had a background in his comprehensive knowledge of the various medical sciences; he made application of them whenever the necessity arose."[6]

At the age of seventy-four the mellowed scholar dominated German medicine. He continued to lecture at the Institute. "The afternoon lectures scheduled in the university catalogue to last forty-five minutes were really of varying and uncertain length, for the master, wandering in the boundless field of his knowledge and experience, could never quite conform to a limit set by a clock until the present discussion had been completed in every detail. . . A part of almost every lecture was given over to a consideration of etymology; so profound a scholar of the classical languages was he as to be always able to explain and justify a terminology often at variance with current usage. One came to feel that these discourses were a source of liberal education along more lines than one.

Every man who heard the lectures on general pathology, during which specimen jars were passed, will recall with a smile the caustic protest which escaped that master of invective whenever a thoughtless student (German

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*See Minnesota Med 49:359, 1966.

Continued

usually) tilted the container until preserving fluid touched glue that held on the lid. The luckless one at once was favored with certain and always the same A. B. C.'s that underlie the solubility of glue while a hundred delighted eavesdroppers endeavored to keep their own emotion within reasonable bounds, and why not, said those who realized that for forty years the lecturer himself had with his own hands been gluing on those covers by the thousands and pasting the labels which bore his own precise inscriptions."[7] By 1886 his collected specimens had reached the huge number of approximately 17,000.

"His professional activities continued unabated until his eightieth birthday found him still in full possession of all his faculties, able to appreciate and enjoy to the full a national holiday in his honor, official testimonials from governments or scientific societies of every land in which medicine is taught and the great gold medal of science from the Kaiser himself."[8]

The theory of pathology was given great impetus by Virchow during his lifetime, and although he made many other discoveries not only in pathology but also in anthropology and archaeology, it is by his cellular pathology that his name will live.

References

5. Long, Esmond R.: A History of Pathology, Williams & Wilkins, 1928, p. 200.
6. Bartlett, Willard: Mayo Foundation Lectures on the History of Medicine, A Sketch of Virchow's Life and Time, W. B. Saunders, 1933, p. 466.
7. Ibid, p. 469.
8. Ibid, p. 478.

Etymologically Speaking

Drug — from Low German droge vate (dry casks) in which droge (dry) was wrongly taken to be a designation of the contents. (Webster)

The word "drug" means something that is dried to be kept for future use. The term came to be limited to the dried herbs that were gathered for the cure of disease. After a time its meaning was extended to include minerals and animal products that were thought to have a curative effect, corresponding to that of the dried plants. The development of the significance of the word did not end there. Probably the most interesting reflection for us on the word "drug" is to be found in the use of it to indicate something that has lost its value and is no longer salable. We say that things are "a drug on the market" when nobody wants to buy them. Evidently this usage came from the fact that so many materials, which for a time had had a great vogue and abundant sale because they were thought to produce wonderful curative effects, failed after a time to do any good and thus became quite literally "drugs on the market." This is etymology's rather pessimistic bit of humor with regard to drugs and their rise and fall in popularity and vendibility.

— James Walsh, M.D., Ph.D., Sc.D.: Cures, 1924.

Character is like a tree and reputation like its shadow. The shadow is what we think of it; the tree is the real thing. — Lincoln

A gentleman will not insult me, and no man not a gentleman can insult me.
— Frederick Douglas

Meetings and Announcements

There is no dispute managed without passion, and yet there is scarce a dispute worth a passion. — Sherlock

MARCH

Minnesota Society of Anesthesiologists annual business meeting, March 11, Minneapolis. Plans to be announced. Contact: V. S. Lawrence, M.D. 330-3997.

New York Academy of Sciences conference on "Pediatric and Adolescent Gynecology, March 24-26, Waldorf-Astoria, New York. Contact Warren R. Lang, M.D., 1025 Walnut Street, Philadelphia.

Department of Otolaryngology of the University of Illinois postgraduate course in laryngology and bronchoesophagology, March 21-April 2. Write: College of Medicine, University of Illinois, Postoffice Box 6998, Chicago.

American Medical Association Air Pollution Medical Research Conference, Los Angeles, Ambassador Hotel, March 2-4. Contact AMA Office.

St. Louis County Medical Society meeting March 10, 8:00 p.m. St. Mary's Hospital, Duluth. Executive Committee Meeting at 6:00 p.m.

Twin City Urological Society Meeting, March 18, 6:00 p.m., Town and Country Club, St. Paul.

Ramsey County Medical Society Meeting, March 28, 8:00 p.m., 1500 Lowry Medical Arts Building, St. Paul.

Hennepin County Medical Society meeting, March 7, 6:00 p.m., Pick-Nicollet Hotel, Minneapolis.

Hennepin County Psychiatric Society meeting to be held in connection with the Hennepin County Medical Society meeting.

Minnesota Academy of Medicine meeting, March 9, 6:30 p.m., Town and Country Club, St. Paul.

APRIL

Minnesota Academy of General Practice meeting of House of Delegates, Hotel Radisson in Minneapolis, April 12, and annual refresher on April 13-14.

Minnesota Academy of Medicine meeting, Town & Country Club, St. Paul at 6:30 p.m., April 13.

St. Louis County Medical Society executive committee meeting, 6:00 p.m. regular meeting, 8:00 p.m., St. Luke's Hospital, Duluth, April 14.

Twin City Urological Society meeting, Town & Country Club, St. Paul, 6:00 p.m., April 15.

Ramsey County Medical Society meeting, 1500 Lowry Medical Arts Building, St. Paul, 8:00, April 25.

ANNOUNCEMENTS

Dr. Birger Strandell, a member of the faculty of the Caroline Institute, Stockholm, and editor of ACTA MEDICA SCANDINAVICA, will lecture on "Linnaeus" at Rochester, May 10, 1966. The lecture, sponsored by the Mayo Foundation chapter of Sigma XI, will be held a day before the opening of the annual meeting of the American Association for the History of Medicine. Contact: Thomas E. Keys, 200 First Street Southwest, Rochester, Minnesota.

* * *

The twenty-ninth annual meeting of The New Orleans Graduate Medical Assembly will be held March 7, 8, 9 and 10, 1966, headquarters at The Roosevelt Hotel. Presentations will be of interest to both specialists and general practitioners. This program is acceptable for twenty-nine (29) accredited hours by the American Academy of General Practice, Write Secretary, New Orleans Graduate Medical Assembly, 1430 Tulane Avenue, Room 1528, New Orleans, Louisiana 70112.

* * *

Mayo Clinic and Mayo Foundation clinical reviews, March 28-30 and April 4-6, Mayo Civic Auditorium, Rochester, Minnesota. Limited attendance. Contact: M. G. Brataas, Mayo Clinic, Rochester.

* * *

A symposium on Liver Disease will be held in the Mayo Auditorium of the University of Minnesota May 23, 24 and 25, in honor of Cecil James Watson, M.D. Symposium is open to all physicians at no charge.

* * *

Spring Cardiopulmonary Seminar will be held at Mount Sinai Hospital, May 19, 20. Contact: Jerome T. Grismer, M.D., Mt. Sinai Hospital, Minneapolis.

* * *

Minnesota State Medical Association Meeting, May 16-17, St. Paul Hotel, St. Paul. Contact: Harold W. Brunn, Executive Secretary, 496 Lowry Medical Arts Building, St. Paul.

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Contraindications: Contraindicated in individuals who have shown hypersensitivity to any of its components. Not recommended for prophylaxis or in the management of infectious processes which may require more than 10 days of continuous therapy. If clinical judgement dictates therapy for longer periods, serial monitoring of liver function is recommended. Not recommended for subjects who have shown abnormal liver function tests, or hepatotoxic reactions to triacetyloleandomycin.

Precautions and Adverse Reactions: Triacetyloleandomycin, administered to adults in daily oral doses of 1.0 gm. for 10 or more days, may produce hepatic dysfunction and jaundice. Adults requiring 3 gm. of Signemycin initially should have liver function followed carefully and the dosage should be reduced as promptly as possible to the usual recommended range of 1.0 to 2.0 gm. per day. Present clinical experience indicates that the observed changes in liver function are reversible after discontinuation of the drug. Use with caution in lower than usual doses in cases with renal impairment to avoid accumulation of tetracycline and possible liver toxicity. If therapy is prolonged under such circumstances, tetracycline serum levels may be advisable. In long term therapy or with intensive treatment or in known or suspected renal dysfunction, periodic laboratory evaluation of the hematopoietic, renal and hepatic systems should be done. Formation of an apparently harmless calcium complex with tetracycline in any bone forming tissue may occur. Use of tetracycline during tooth development (3rd trimester of pregnancy, infancy and early childhood) may cause discoloration of the teeth. Reversible increased intracranial pressure due to an unknown mechanism has been observed occasionally in infants receiving tetracycline. Glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis and definite allergic reactions occur rarely. Severe anaphylactoid reactions have been reported as due to triacetyloleandomycin. Photosensitivity and photoallergic reactions (due to the tetracycline) occur rarely. Medication should be discontinued when evidence of significant adverse side effects or reaction is present. Patients should be carefully observed for evidence of overgrowth of nonsusceptible organisms including fungi, which occurs occasionally, and which indicates this drug should be discontinued and appropriate therapy instituted. Steps should be taken to avoid masking syphilis when treating gonorrhea.

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1. Schleif, R.H.: J.A.PH.A., 46:179,1957 *U.S. Pat. No. 3,062,714

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Contraindications: Benactyzine hydrochloride is contraindicated in glaucoma. Previous allergic or idiosyncratic reactions to meprobamate contraindicate subsequent use.

Precautions: *Meprobamate*—Careful supervision of dose and amounts prescribed is advised. Consider possibility of dependence, particularly in patients with history of drug or alcohol addiction; withdraw gradually after use for weeks or months at excessive dosage. Abrupt withdrawal may precipitate recurrence of preexisting symptoms, or withdrawal reactions including, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, the dose should be reduced and operation of motor vehicles or machinery or other activity requiring alertness should be avoided if these symptoms are present. Effects of excessive alcohol may possibly be increased by meprobamate. Grand mal seizures may be precipitated in persons suffering from both grand and petit mal. Prescribe cautiously and in small quantities to patients with suicidal tendencies.

Side effects: Side effects associated with recommended doses of 'Deprol' have been infrequent and usually easily controlled. These have included drowsiness and occasional dizziness, headache, infrequent skin rash, dryness of mouth, gastrointestinal symptoms, paresthesias, rare instances of syncope, and one case each of severe nervousness, loss of power of concentration, and withdrawal reaction (status epilepticus) after sudden discontinuation of excessive dosage.

Benactyzine hydrochloride—Benactyzine hydrochloride, particularly in high dosage, may produce dizziness, thought-blocking, a sense of depersonalization, aggravation of anxiety or disturbance of sleep patterns, and a subjective feeling of muscle relaxation, as well as anticholinergic effects such as blurred vision, dryness of mouth, or failure of visual accommodation. Other reported side effects have included gastric distress, allergic response, ataxia, and euphoria.

Meprobamate—Drowsiness may occur and, rarely, ataxia, usually controlled by decreasing the dose. Allergic or idiosyncratic reactions are rare, generally developing after one to four doses. Mild reactions are characterized by an urticarial or erythematous, maculopapular rash. Acute nonthrombocytopenic purpura with peripheral edema and fever, transient leukopenia, and a single case of fatal bullous dermatitis after administration of meprobamate and prednisolone have been reported. More severe and very rare cases of hypersensitivity may produce fever, chills, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, anaphylaxis, stomatitis and proctitis. Treatment should be symptomatic in such cases, and the drug should not be reinstituted. Isolated cases of agranulocytosis, thrombocytopenic purpura, and a single fatal instance of aplastic anemia have been reported, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity has been reported, usually after excessive meprobamate dosage. Suicidal attempts may produce lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

Dosage: Usual starting dose, one tablet three or four times daily. May be increased gradually to six tablets daily and gradually reduced to maintenance levels upon establishment of relief. Doses above six tablets daily are not recommended even though higher doses have been used by some clinicians to control depression and in chronic psychotic patients.

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Physician's Diary

If you would civilize a man, begin with his grandmother. — Victor Hugo

Dr. **Reuben Berman** of Minneapolis is the newly elected president of the Minnesota Heart Association. Other newly elected officers are: **Dr. Ivan D. Frantz, Jr.** of St. Paul, president-elect, and **Dr. John L. Juergens** of Rochester, Secretary.

* * *

Two scientific exhibits, both by University of Minnesota physicians, won gold medal awards at the 24th Annual Meeting of the American Academy of Dermatology in December. A research team headed by **Dr. Alvin S. Zelickson** of Minneapolis, was awarded the highest honor for original work. **Dr. Zelickson** and **Dr. R. L. Coupe** also reported on the effect of hydrocortisone on fibroblasts and collagen synthesis. The top award for an exhibit of high teaching value went to a research team headed by **Dr. Ramon M. Fusaro** of Minneapolis.

* * *

The following physicians have been elected to active membership in the American Academy of General Practice: **Dr. Donald Maus** of Monticello, **Dr. John E. Sutherland** of Marshall, **Dr. Gerald Cotton** of Fosston and **Dr. Lois Anselment** of Excelsior.

* * *

NEW LOCATIONS: **Dr. John W. Savaryn** has opened his new Medical Clinic in Waconia . . . **Dr. Bernard Nauth** has opened offices at the PBC Medical Clinic in Brooklyn Center . . . **Dr. Joel Brende** will join **Dr. David McQuoid** in the practice of medicine in Littlefork . . . The Mankato Clinic has added the following physicians to its staff: **Dr. Gail W. Haut**, radiologist, of Price, Utah, **Dr. Joseph A. Heaney**, psychiatrist, from Philadelphia, and **Dr. H. C. Labrec**, dermatologist, from LaCrosse, Wisconsin . . .**Dr. Jack Naros** has joined the Crosby Clinic . . . **Dr. L. E. Stover** of Waseca will join **Drs. K. A. Peterson, J. E. Eckdale** and **John E. Sutherland** in Marshall . . . **Dr. M. Doebler** of Mora is the new medical director of the Armour Company in St. Paul . . . **Doctors Emil Johnson** of Stillwater and **Dr. William Thomas** of Long Lake will open offices in Minnetonka Village . . . **Dr. John Marso** is associated with **Dr. George E. Penn** in the practice of obstetrics and gynecology in Mankato.

Burtrum Schiele, M.D., professor in the department of Psychiatry of the University of Minnesota, received an unrestricted grant for medical research from Wyeth Laboratories.

* * *

Doctors Robert L. Scanlan, Roger E. Cupps, Albert L. Rhoton, Ronald J. Forth, Edward G. Rosenow, III, Virgil Fairbanks, Dan E. Tolman, Charles C. Kennedy, Francoise M. Garney, Bruce A. Lund and **James W. Linman** have been appointed as consultants to the staff of the Mayo Clinic, Rochester.

* * *

Dr. W. J. Kozel of Morris was elected president of the West Central Minnesota Medical Society at its recent meeting. **Dr. R. A. Rossberg** of Morris was elected vice-president, and **Dr. H. C. Winge** of Wheaton was elected secretary.

* * *

Dr. C. L. Sheedy, after thirty-nine years in the practice of medicine in Austin, will leave that city to work in the out-patient clinic at the Veterans Administration at Fort Snelling.

* * *

Fourteen doctors from the College of Medical Sciences at the University of Minnesota participated in the 15th annual meeting of the American College of Cardiology in February. They were: **Doctors G. W. Lyons, W. G. Manax, R. H. Dietzman, R. C. Lillehei, Robert S. Eliot, Randolph M. Ferlic, C. Walton Lillehei, Robert D. Sellers, Frank Quattlebaum, Hiroshi Mizukami, Ernest Simonson, Noboru Okamoto, Suraj Ahuja** and **George W. Manning.**

* * *

Dr. Warren H. Ruchie has been named chief-of-staff of the Rice Memorial Hospital in Willmar. **Dr. L. Munneke** of Clara City is the vice-chief of staff, and **Dr. J. N. Kvale** of Atwater, is the secretary.

* * *

Ramsey County Medical Society new officers are: **Dr. Brian McGroarty**, president, **Dr. John Earl**, president-elect, and **Dr. William Hollinshead**, secretary.

The Doctor and Literature

(Continued from page 408.)

Arrowsmith displays Lewis at the height of his creative powers. Then followed a long, slow, decline artistically and morally. Lewis divorced Grace and married Dorothy Thompson, by whom he had a son, Michael.

Incidentally, Michael Lewis appeared in St. Paul as Henry VIII in *A Man For All Seasons* in September, 1963.

Sinclair Lewis had a peculiar need for human companionship with a corresponding inability to support real human relationships. Both Grace and Dorothy wrote bitterly of him and his mistress Marcella Powers, who left him in disgust.

Sinclair Lewis lost every friend he ever had because of his boorishness and ingratitude for the many kindnesses he had received from their hands. He died alone on January tenth, 1951, in a Catholic Hospital in Rome of delirium tremens.

The genesis of his masterpiece *Arrowsmith* is interesting. Dr. Morris Fishbein introduced Lewis to Paul de Kruif, a microbiologist.

Conversation with De Kruif inspired Lewis to write a novel about a young doctor, Martin Arrowsmith, starting out as a general practitioner and developing into a reserach scientist, scorning cheap and easy success. De Kruif provided the medical and scientific information Lewis required. Doctor and novelist travelled through Europe seeking background atmosphere and character types for the novel.

After four years of intensive research and creative effort, *Arrowsmith* was published in March, 1925. It was nominated for the Pulitzer Prize, which Lewis, ever the rebel, refused on the grounds the Pulitzer Committee was trying to dictate the standards to which American writers must conform. *Arrowsmith* won world-wide critical acclaim.

> "The humanity of it outshines the science. It has a stirring epic quality. . ."

praised the *London Times*. Helen Hayes, the late Ronald Colman, and Myrna Loy, starred in the motion picture version of the novel in 1932.

The theme of the novel is the struggle of Martin Arrowsmith between being a well paid slave in the McGurk Institute and embracing a dedicated career devoted to pure research unhampered by the insistent demands for immediate results, by Doctor A. DeWitt Tubbs, director of the institute.

Martin resolves his inner struggle and conflict by leaving his wealthy second wife, Joyce, his well paid post at the McGurk Institute, to go off with his friend, Terry Wickett and devote the rest of his life to pure research.

Arrowsmith sums up his dedication to knowledge for knowledge's sake in the prayer:

> "God give me unclouded eyes and freedom from haste. God give me a quiet and relentless anger against all pretense and all work left slack and unfinished. God give me a restlessness whereby I may neither sleep or accept praise until my observed results equal my calculated results. God give me strength!"

Reverend Edward Keenan
St. Paul, Minnesota

A well-known philosopher has written: "Every man would like to be God if it were possible; some few find it difficult to admit the impossibility."

— Rev. Chester Tulga, Moody Monthly

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WANTED: Board Certified or eligible internist to associate with group in large, active practice in Minneapolis. Group consists of Surgeon, Obstetrician, Pediatrician and Internist maintaining downtown and suburban offices. Partnership in mind. Contact: Jesse J. Barron, M.D., 1127 Medical Arts Building, Minneapolis, Minnesota 55402, FEderal 2-8259.

OLD, WELL ESTABLISHED multi-specialty group of 23 doctors in Midwestern city has opening for board certified or eligible specialists as follows: orthopedic surgeon, internist, pediatrician, otolaryngologist. All departments established and growing. Well-equipped clinic and excellent hospital facilities in community. Attractive financial plan leading to full partnership. Include curriculum vitae. Full expenses paid for applicants invited for interview. Write: MINNESOTA MEDICINE — 337; 496 Lowry Medical Arts Building, St. Paul 55102.

BUSY, GROWING aggressive 3-man partnership in Northwest Wisconsin serving a trade area of 15,000 needs a well-trained recent graduate with fulfilled military obligations to associate immediately on excellent salary, with partnership in 1 year if mutually agreeable. Modern 15 room air conditioned brick clinic building is being doubled in size this year. 32 bed hospital and new 42 bed nursing home one minute from clinic. New 1500 student consolidated school. Excellent hunting, fishing and outdoor sport facilities in immediate area. Contact: MINNESOTA MEDICINE — 317; 496 Lowry Medical Arts Building, St. Paul 55102.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with early partnership. Write: MINNESOTA MEDICINE — 289; 496 Lowry Medical Arts Building; St. Paul, 55102.

WANTED: Generalist to associate with two man partnership in Northern Minnesota. Community has a thirty-seven bed hospital, X ray and laboratory technicians and nurse anesthetist. Good hunting and fishing. Adequate salary and time off. Contact: A. G. Janecky, M.D., Baudette Clinic, Baudette, Minnesota.

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GENERAL PRACTITIONER WANTED: to associate with physician-surgeon in Owatonna, a Southern Minnesota community, 25,000 population. Clinic building three years old; with five large treatment rooms, lab.; x ray; central supply; two doctors' offices; pharmacy; and business offices. Located next door to 85-bed city hospital. Good opportunity for partnership. Contact: O. W. Roberts, M.D.; 920 South Cedar Street; Owatonna, Minnesota. Phone 451-4630.

MEDICAL ART. Drawings, charts and lettering for publication, slide lectures, movies, exhibits and television. Also three dimensional models. Al Hage — 339-1012, Minneapolis.

WANTED — Internist, board certified or qualified, to associate with two board certified internists. Ten man multi-specialty group. (Lenont Peterson Clinic, Virginia, Minnesota) — Heart of the expanding taconite industry.

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WANTED: young general practitioner to join six-man group consisting of 4 GPs, a general surgeon, and radiologist. College town of 5,500, 30 miles from Twin Cities. Also need LOCUM TENENS in general practice. Contact: Ed Jenkins, Mgr., River Falls Medical Clinic, River Falls, Wisc. Phone 425-5322.

WANTED: Immediate opening for young GP in an established medical corporation. Three man G.P. group located in rapid-growing North Suburban Metropolitan Area. 15 minutes from loop and large educational center. New clinic. New 150-bed hospital. Salary open, fringe benefits. Fridley Medical Center, P.A., 203 Mississippi Street, Minneapolis, Minnesota 560-2950.

FOUR STAFF ADDITIONS to Southern California Group of 24 physicians. Internist with chest subspecialty, ophthalmologist, otolaryngologist, general practitioner. Partnership possibility after first year. Administrator, Gallatin Medical Group, 10720 S. Paramount Blvd., Downey, Calif.

WANTED: Young internist and pediatrician, board certified or eligible, to join 6-man group consisting of 4 GP's, a general surgeon, and a radiologist. College town of 5,500 only 30 miles from Twin Cities. Salary open with early partnership opportunity. Write or call collect: Ed Jenkins, Mgr., River Falls Medical Clinic, River Falls, Wisc., phone 425-5322.

Continued

EXCELLENT and immediate opening for one or two physicians. 17-bed fully-equipped municipal hospital with lab and x-ray facilities. Also private 40 bed nursing home. Complete clinic, including equipment, available for rent. Doctor owner retiring because of ill health. No investment needed. Prosperous agricultural community. Opportunity for rewarding lifetime practice. Phone 669-4421 collect, Clarkfield, Minnesota Hospital.

WANTED: General practitioner able to do surgery. Present physician wanting to "semi-retire." Good community, prosperous farming. Good schools and churches. New hospital and clinic buildings. Contact: Warren Clinic, P.O. Box 107, Warren, Minnesota 56762.

WANTED: Young G.P. for rural practice partnership. No initial investment. Previous partner and well-equipped for dual practice. Good hospital — 12 miles and large medical center 30 miles on four lane highway. Small town in stable farming community, resort area, hunting and fishing, good school system. Contact: A. S. Midthune, M.D., Lake Park, Minnesota.

CHIEF OF PSYCHIATRIC SUPERVISORY STAFF needed to help with clinical supervision and teaching in expanding (18 Resident Physicians) fully-approved residence training program. Ideal living in active community in the heart of Michigan's Water-Winter Wonderland. Newly established position requires board certification in psychiatry and additional experience in clinical supervision. Salary range depending upon qualifications, $17,383 to $21,339 with liberal Michigan civil service benefits. Contact Arthur F. Dundon, M.D., Clinical Director, Traverse City State Hospital, Traverse City, Michigan. An equal opportunity employer.

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GENERAL PRACTITIONER — MINNESOTA STATE PRISON. Serve as Medical Director of 50-bed hospital with staff of registered nurses and laboratory technician. Surgical resident provided by University of Minnesota. Consultant service in various specialties also available. Residence suitable for family, furnished free-of-charge. Minnesota Civil Service Position. Contact: Mrs. Barbara Sundquist, Box 55, Stillwater, Minnesota 55082 — Telephone 439-1910, Ext. 320.

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OPPORTUNITY FOR GENERAL PRACTITIONER to join long established four-man clinic in excellent county seat community of 7000 in western Minnesota. Newly expanded quarters with new equipment and furnishings. New hospital and two new rest homes. Attractive salary. Full partner in three years with no financial investment. Contact the Montevideo Clinic, Montevideo, Minnesota.

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WANTED: YOUNG DOCTOR to join an established clinic group. Excellent hospital facilities. Excellent opportunity. WRITE: MINNESOTA MEDICINE — 342, 496 Lowry Medical Arts Building, St. Paul 55102.

WANTED: BOARD ELIGIBLE or certified general surgeon interested in one-year residency in colon and rectal surgery at the University of Minnesota Hospitals. Write to Chairman, Department of Surgery, University of Minnesota Hospitals, Minneapolis 55455.

GENERAL PRACTITIONER — Well established 14 man multispecialty group (seven general practitioners) midwestern city, population 30,000. Beginning salary, then partnership; no investment. Clinic building six years' old; excellent school, hospital and recreational facilities. Write: MINNESOTA MEDICINE — 343, 496 Lowry Medical Arts Building, St. Paul 55102.

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CLINIC LOCATION across from Knollwood and Target Stores. Ample ground and parking space. Will build and lease for interested group, or sell. J. Russell Carroll, 17 Tenth Avenue South, Hopkins, Minnesota. 935-4468.

UNOPPOSED GENERAL PRACTICE available June 1, 1966 in South Central Minnesota (Blooming Prairie, population 1850). This area provided deferment for active young MD during World War II. Leaving to specialize. Contact: John R. Fischer, M.D., Blooming Prairie.

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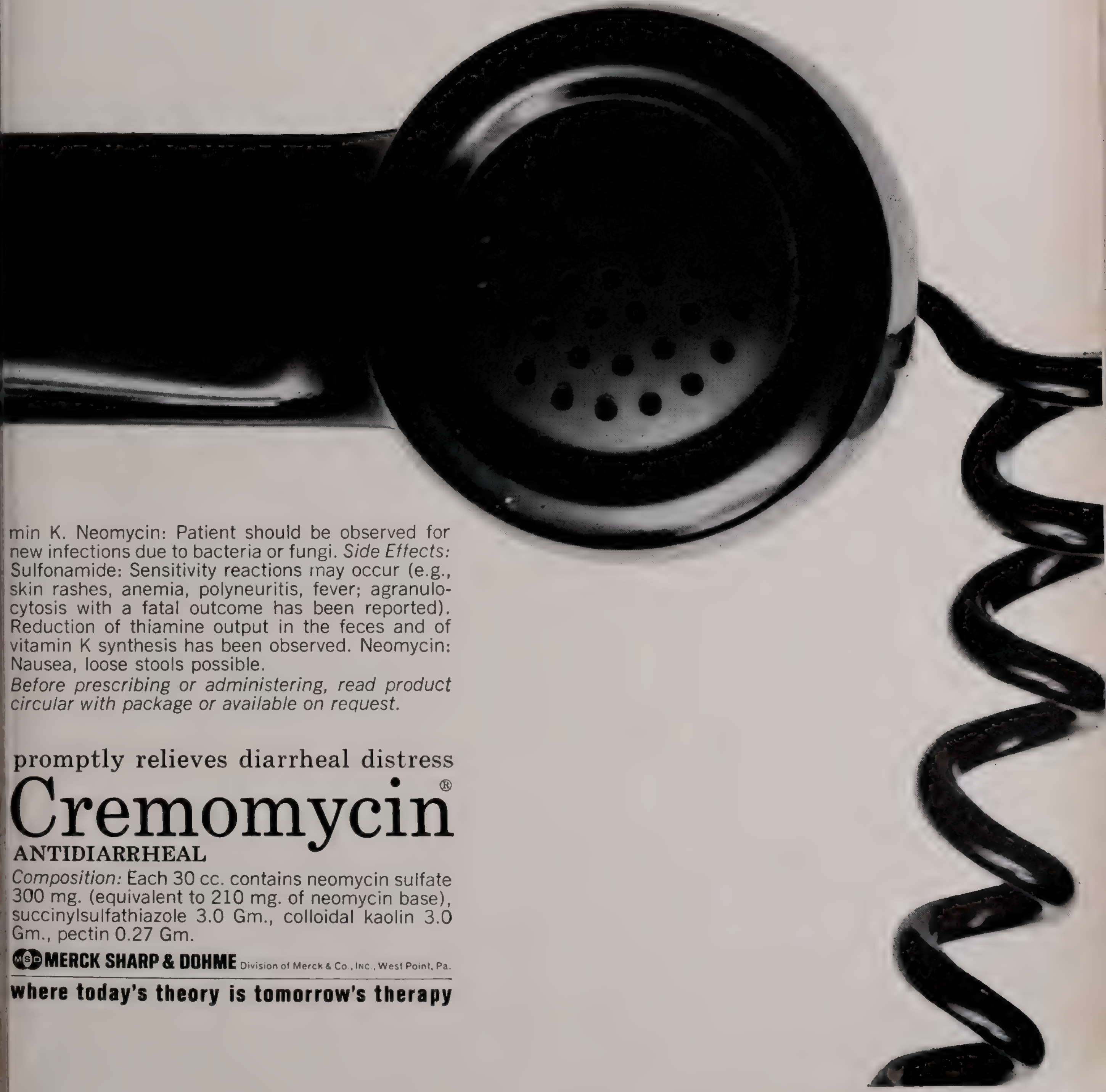

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Minnesota Medicine at a Glance

The Incompetent Cervix — Stromme et al. Page 393

Incompetent cervix, an important cause of second trimester pregnancy wastage, may be of congenital or traumatic origin. Prophylactic or therapeutic cervical cerclage using the Shirodkar technique reduced pregnancy wastage from this defect from 80% to 20% in a series of 51 patients. The technique is simple and carries virtually no risk to the patient or the fetus. Delivery subsequent to cerclage may be vaginal or abdominal depending upon the type of material used.

Profunda Femoris-Popliteal Shunt — Farley et al. Page 400

There are occasions when a vein autograft or bypass procedure, which has been done to revascularize an arteriosclerotic extremity, fails and reoperation becomes necessary. In the hands of Farley et al. an alternative procedure, wherein the saphenous vein is removed and reimplanted, providing an anastomosis between the profunda femoris and the popliteal arteries avoids the previous surgical procedure by making a medial approach. They have found two advantages to this approach and have encountered no disadvantages.

Cardioversion of Ventricular Tachycardia — Aberg and Swenson Page 403

Ventricular tachycardia is a serious complication of myocardial infarction. Doctors Aberg and Swenson report four cases of ventricular tachycardia following myocardial infarction successfully treated with cardioversion.* This complication, particularly in seriously ill patients, requires immediate diagnosis and therapy. Cardioversion is suggested as the method of choice of therapy in such cases as these. In the four cases reported, all survived, with one dying subsequently, two months after discharge from the hospital.

Unusual Organism for Acute Cholecystitis — DeShazo et al. Page 409

Coagulase positive staphylococcus as a cause of acute cholecystitis is ordinarily not encountered as one of the etiologic organisms. A well documented case is herein recorded.

Brain Scanning — Wigdahl et al. Page 411

Brain scanning with radioactive isotopes, Mercury 197, is a simple, safe, highly efficient procedure to detect brain lesions, such as malignant, primary or metastatic neoplasms, non-neoplastic lesions, such as intracranial, subdural hematoma or large brain infarcts. The authors performed 432 brain scans, 338 of which were diagnostic. Of the 45 primary brain tumors encountered in this series, approximately 85% revealed a positive brain scan. About 80% of the metastatic brain tumors revealed a positive scan. Thirty positive scans of non-neoplastic lesions were encountered, one-half of which were due to cerebrovascular disease.

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*See Test Your Word Score Page 447.

Ulcerative Colitis in Children — Lynn Page 417

The problem of ulcerative colitis in children, though a grave disease, need not be entirely without hope.

In the emergency treatment when the patient is in extremis the simplest possible, double-barreled ileostomy may be sufficient; but whenever it is possible, removal of the distal ileum and a portion of the colon is indicated.

When the period of election has arrived, then a permanent ileostomy and total colectomy can be planned. Before doing this it has been found to be of value to have the patient wear an ileostomy bag in order to find the most suitable place for the ileostomy, and in some instances psychiatric therapy may be indicated. In order that the patient, the referring physician, and the parents be adequately prepared both physically and emotionally, the attending surgeon should be more aggressive in explaining the value of definitive procedures in a life to be lived with a permanent ileostomy.

Predicated on his experience that ulcerative colitis beginning in childhood is very serious from every viewpoint (longevity, cancer, perforation, invalidism, etc.) the author makes a strong plea for earlier surgical extirpation accompanied by permanent ileostomy.

Cystic Dilatation of the Common Duct — Carlson and Glas Page 429

Cystic dilatation of the common duct is relatively rare but may be encountered, and it is therefore well for any surgeon to have in mind the most desirable procedure for the alleviation of the symptoms of this disease. If the diagnosis can be established, the relatively simple procedure of choledochocysto-duodenostomy, as illustrated, can be advantageously reviewed.

The Penicillins — *Medical Seminar* —
Graduate School of Medicine, Mayo Clinic Page 479

Current clinical areas of interest in penicillin therapy include the following: the development and application of the semisynthetic penicillins; the use of massive doses of penicillin G in gram-negative bacterial infections; the significance of resistant staphylococcal carriers who acquire streptococcal pharyngitis; the relative increase in resistance to penicillin G of some strains of gonococci; the use of penicillin in tetanus prophylaxis in the unimmunized person to avoid the hazards of antitoxin; the use of steroids in continuing penicillin therapy in those who manifest allergy to penicillin; the continuing problem of the nasal carrier of staphylococcus and hospital-acquired infection; and the emergence of increasing strains of sulfa-resistant meningococci, making penicillin the drug of choice in these infections.

Despite the problems of allergic reactions and resistant staphylococci, the penicillins remain drugs of great importance. After years of intensive use, penicillin G is still essentially effective against the same organisms and diseases that confronted it 25 years ago. The development of the semisynthetic penicillins has to some extent countered the problem of resistant staphylococcal infections and has broadened the mode of administration and, in some instances, the spectrum of activity of the penicillins.

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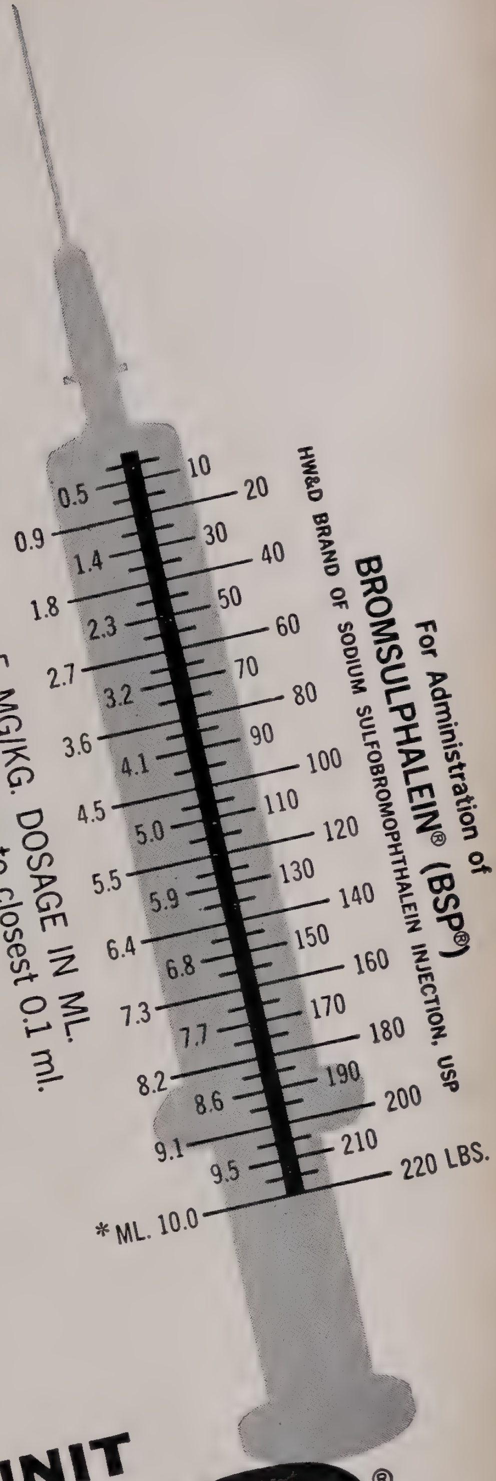

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STATE MEDICAL ASSOCIATION

Volume 49

Number 4

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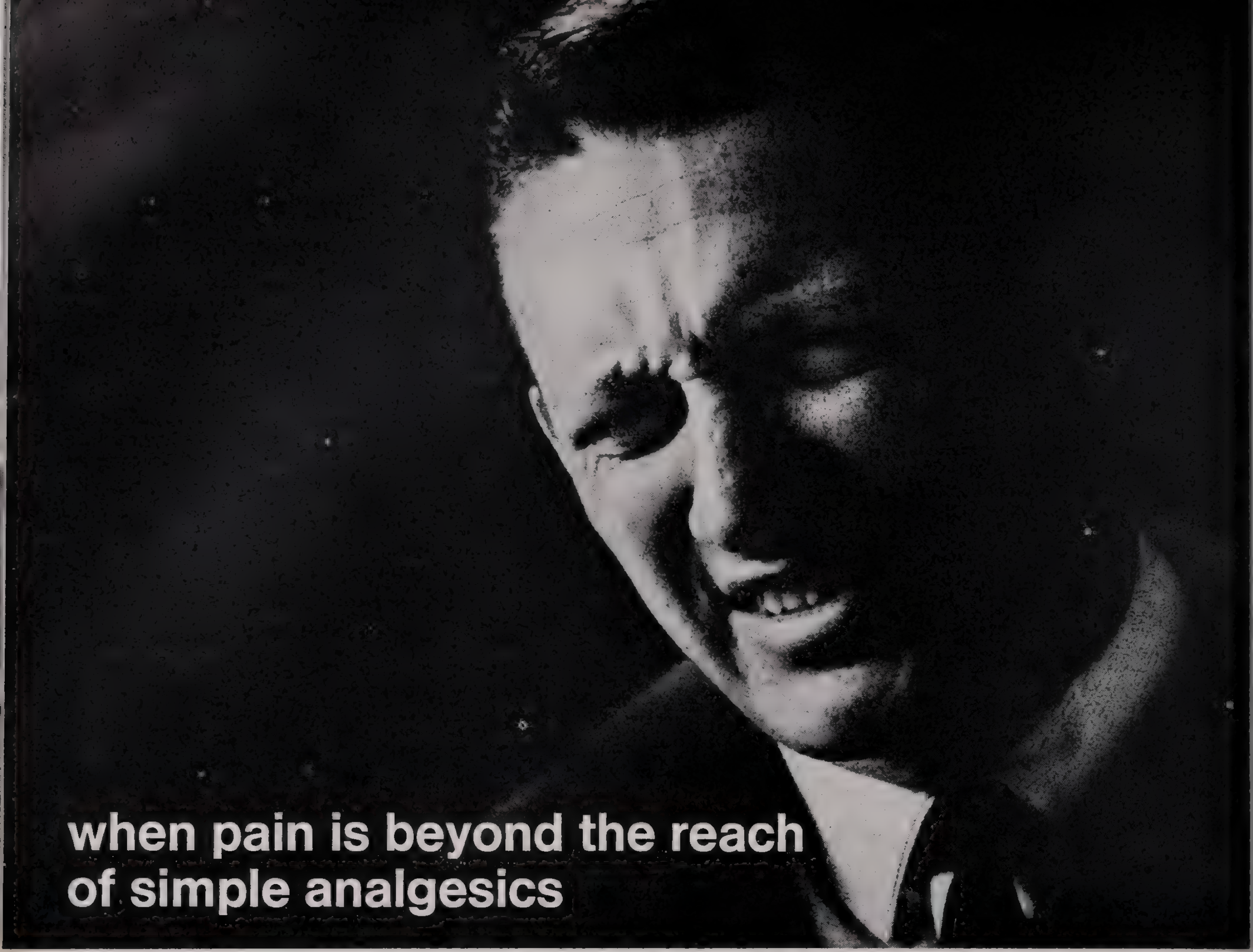
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1. Collective studies, Department of Medical Research, Winthrop Laboratories.

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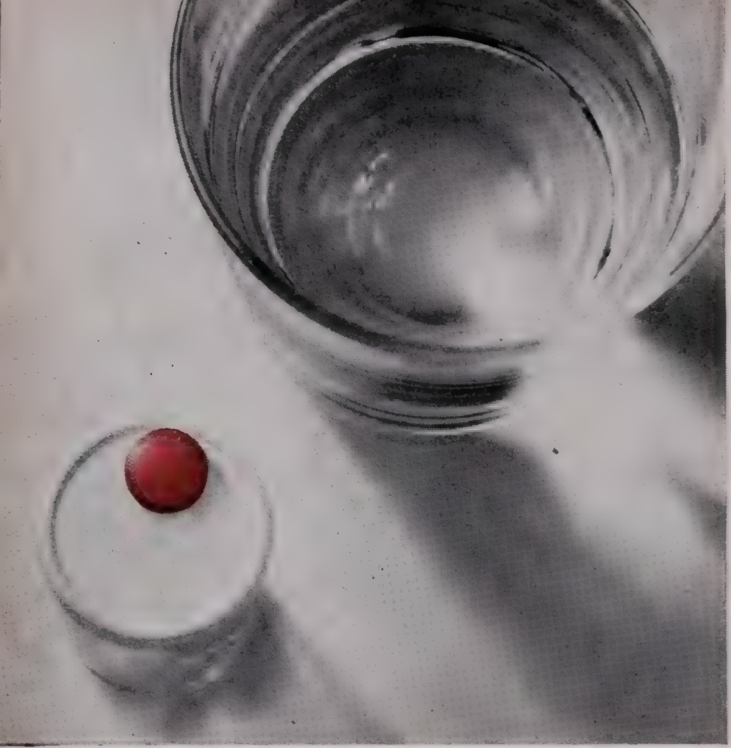

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President's Letter

Again, the time of the Annual Session of the Minnesota State Medical Association is rapidly approaching. This year, meeting in St. Paul on May 16th and 17th, a very representative clinical program has been developed, directed toward the multiple interests of Minnesota physicians, and concerned basically with an appeal, in some area, to every physician's interest.

No program can develop, in the limited time available, a stimulus to attendance at all of the varied presentations on the program, but by the incorporation in the total program of specialty groups, every physician can benefit by participation in the field of his major interest. The speakers will be highly qualified, recognized authorities and representative of medicine in the nation.

Over and above the clinical program, however, is the possibility of physician participation in the other areas in which an Association such as ours must operate. Beginning with the County Societies, and expanding to the State Association, there is always a feeling on the part of some physicians that their personal feelings about policy, procedures and official position are not properly represented by the Association. In essence, this is true of every organization, medical, political, religious or industrial. In the area of medical practice where individualists are the rule, it may be more obvious than in any other field, but the opportunity for personal expression of dissent is greater in organized medicine than in any of those other areas.

Regrettably, this opportunity is too infrequently used. Any dissension expressed in a hospital coffee shop or doctor's cloak room, any disagreement ventilated to fellow physicians, any withheld opinions which lead the holder to nonparticipation in local, county or state determination of policy, are basically an evasion of responsibility.

While it is true that policy is determined by the expressed attitude of the majority, the opinion of every member of this Association is invited, and the consideration of that opinion is never cursory, nor disregarded.

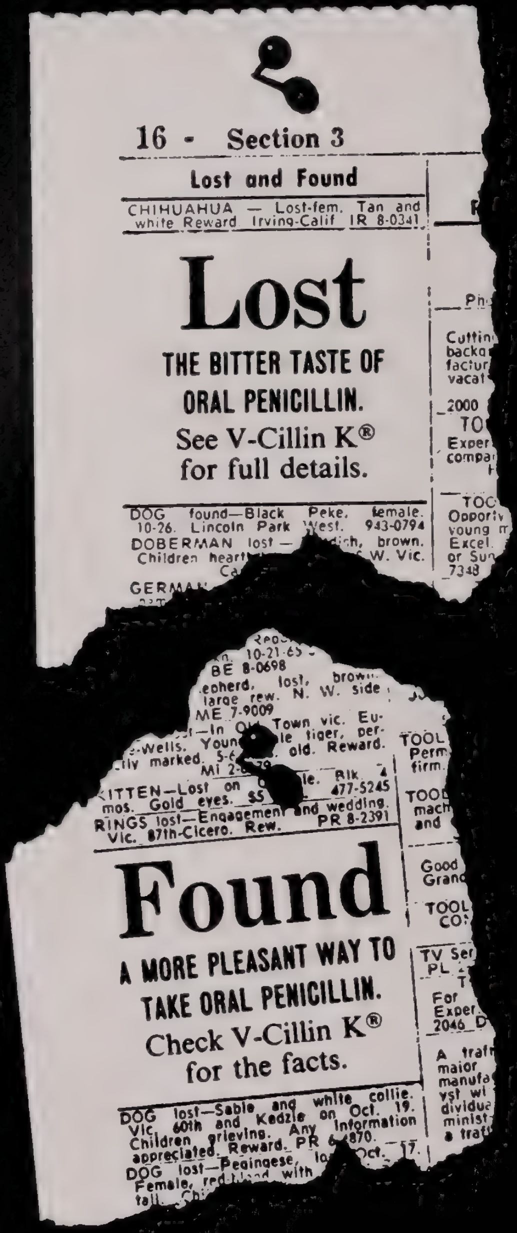
An obligation of the Association has always been a full consideration of member opinion. The attitude of the Council has always been attention to opinion, individual, group or organizational. The Council would fail in its responsibility if all viewpoints were not considered and would be derelict in duty if Council action failed to represent the consensus.

In these trying times, and at this session, the attention of every physician is directed to the opportunity to voice his opinion of the path medicine is following. The reference committees of the House of Delegates are open to all interested physicians, all of whom are encouraged, even urged, to attend and to contribute to these policy proposing hearings.

Never before in the history of medicine has there been a greater need for full physician participation in determining medical policy; never before has there been a greater need for unified physician position, and never before has there been so demanding a recognition by physicians of their strength as a group and their inherent weakness as individuals.

Present planning of this medical program includes an opportunity to hear and question a representative of the Social Security

Continued to page 565.



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Office Management of Hearing Problems

JEROME A. HILGER, M.D.
St. Paul, Minnesota

EIGHTEEN MILLION AMERICANS suffer from handicapping hearing loss. The number of sufferers per thousand of population is on the increase. Only arthritis exceeds hearing handicap as a cause of chronic disability in the over-65-years age group (178 with hypacusis per thousand oldsters). The hearing handicapped, quite reasonably, expect their disability to be appreciated and, at least preliminarily, assessed by their personal physician. Intelligent evaluation is within the purview of an interested practitioner. A constructive inquiry assures the problem medical supervision rather than disposing of it to the exploitation of purely commercial or more charlatan interests.

In this most sociable world adults are readily aware of hearing loss even when only moderate. The occasional complacent victim is made well aware by his associates. Children, on the contrary, are frequently uncomplaining or oblivious to hearing impairment. Poor speech patterns, faulty reaction to sound, and school screening programs are the common identifiers of childhood hearing deficiency.

Causes of Impaired Hearing

Otoscopic examination of the patient with a hearing problem readily demonstrates a sound-obstructing mass if present in the external canal.

Retained Cerumen

A retained cerumen mass is a common and sometimes tedious problem. Manual removal with a small "loop" or spud is preferable if the patient has a known ear drumhead defect or if one is suspected from a history of chronic ear discharge. "Lytic" agents to dissolve cerumen can result in more mischief than aid because of skin irritation or canal fundus fouling. Careful irrigation with the traditional cerumen syringe or an irrigation

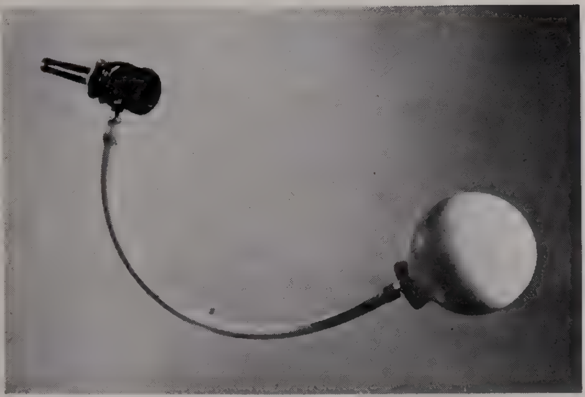

Fig. 1 — Pneumatic speculum tests drumhead mobility.

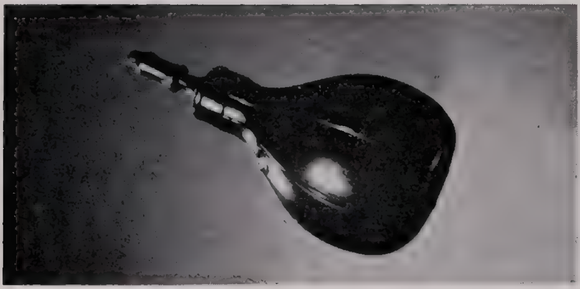

Fig. 2 — Compression bulb for transnasal middle ear inflation.

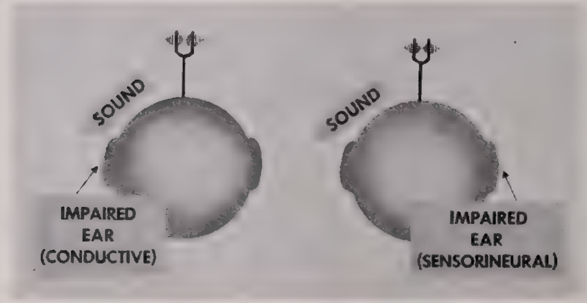

Fig. 3 — Lateralization test for determination of conductive vs. sensorineural hearing impairment.

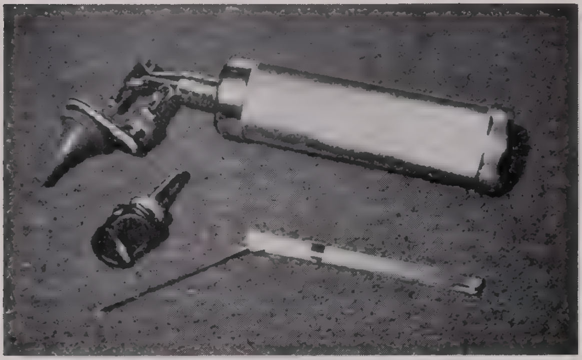

Fig. 4 — Equipment for diagnostic myringotomy.

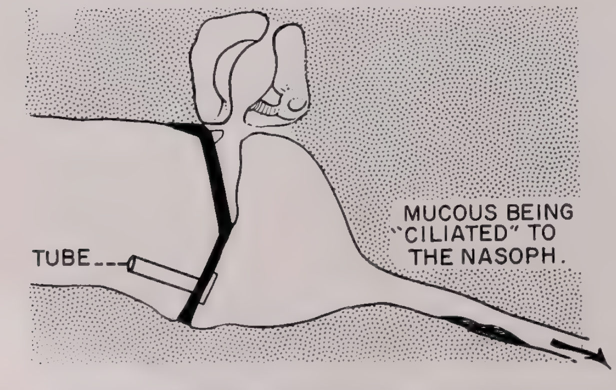

Fig. 5 — Microtube technique for assuring long term ventilation of the middle ear chamber.

bottle adapted to a compressed air source is a safe removal technique. Prior softening with hydrogen peroxide drops can be helpful in some cases. If the removal has been traumatic or if there is inflammation of the canal skin, careful drying with an aspirating tip or sterile cotton applicators can be supplemented with a light insufflation of fine boric acid powder with neomycin powder added in a strength of one part of neomycin powder to eight parts of boric acid powder.

Air Chambers of the Middle Ear

In the absence of an immediately visible cause for a hearing complaint a moment's evaluation of the patient will affirm medical interest and point the way to the pathology. Assessment of the conductive mechanism and of the air chamber of the middle ear through the intact drumhead calls for more than simple otoscopic examination. Routine test of drumhead mobility with the pneumatic speculum (Figure 1) develops skill in interpreting the aeration of the middle ear. Simple transnasal bag (Figure 2) inflation of air into the middle ear is informative. Uncertainty calls for resolution with tuning fork tests and sometimes diagnostic myringotomy.

Impaired Conductive Mechanism

The locus of hearing pathology is determinable in a practical way by the 500 cycles per second tuning fork. The function of the sound-conducting system of the external and middle ear as contrasted with the sound-perceiving system of the internal ear and central neural pathways is readily evaluated with this sound source. For the occasional examiner a simple "self-test" will refresh the principle of sound lateralization. With the vibrating fork based on his sinciput or on his central incisor teeth the examiner will, when he occludes one ear canal, note that he has "lateralized" the midline sound source to that ear. Now, when he repeats the test on his patient, he is reminded that "lateralization" of the sound to the patient's poorer ear indicates a conductive system fault in the ear (Figure 3). Similarly, when the vibrating fork is applied to the "mastoid process" at the posterosuperior pinna attachment of the impaired ear it will be heard better or nearly as well as when held to the ear canal orifice. (The normal ear hears the fork approximately twice as long through the air conduction system at the canal as through bone conduction at the mastoid.)

If then the patient lateralizes the sound from the midline fork to his poorer ear it can be reasonably assumed there is fault in the conductive system medial to the observed drumhead. If the latter is mobile and translucent, ossicular dysfunction is the probable hearing fault. By far the most common ossicular disorder is otosclerosis — a lesion of the labyrinthine capsule which can involve and immobilize the stapedial footplate. Surgery can resolve this fault once recognized.

Diagnostic Myringotomy

If, on the other hand, the drumhead is not translucent or is not mobile, diagnostic myringotomy is necessary to determine the presence or absence of middle ear fluid (Figure 4). Myringotomy in the adult is usually practicable without anesthesia if the patient is of a stable temperament. Visualization is obtained with ample light and magnification with a lens otoscope or speculum. The myringotomy blade must be sharp. The discomfort under these circumstances is transient as with a hypodermic injection. The incision with a two-edged, diamond-shaped blade into the posterior inferior drumhead quadrant will allow air bubbles into the fluid-filled middle ear chamber and fluid will be expelled with transnasal air bag insufflation, suction, or alternate pressure change with the pneumatic otoscope. Occasionally a "micro-tube" (Figure 5) of nonreactive material is placed through the drumhead to provide continuous ventilation and shorten an otherwise tedious resolution, thus precluding the necessity of repeated myringotomies. This procedure requires technical experience and excellent visualization with adequate magnification.

The adult with middle ear fluid must have careful nasopharyngeal examination. Inflammatory response to infection or allergy is the usual cause, but carcinoma in the peritubal area causes a fluid-filled middle ear as early evidence in some cases.

For the child, diagnostic myringotomy usually requires the immobility of general anesthesia. "Micro-tubes" through the drumhead are commonly used to further resolution of the reactive middle ear.

Localizing the Pathology

If the 500 cycle per second fork, vibrating on the midline skull, is lateralized to the better hearing ear and away from the poorer ear, the pathology in the poorer ear is in the sensorineural portion of the hearing system (Figure 3). In addition, in the sensorineural defective ear, if the base of the vibrating fork is applied to the mastoid process at the posterosuperior pinna attachment, it will be heard less well than when held at the canal orifice. Preliminary to testing his hearing-impaired patient, the occasional examiner is again well advised to refresh in his mind this relationship by testing his own ear with and without canal occlusion.

A Spectrum of Tuning Forks

When both ears have significant hearing loss, additional tests are definitive. Tests can be quantitative as well as qualitative. Preliminary study of "how much" loss is present can be approximate. Speech tests by whisper techniques have many faults. A watch test by simple distance measurement is unimpressive but gives some useful information when properly compared with a normal. The threshold vibrations of a spectrum of tuning forks (500 and 2000 are key frequencies), when compared with a normal hearing ear, are informative even in uniform ambient room noise. A basic pure tone air conduction audiometer with properly occlusive ear muff receivers provides a better quantitative method for a general diagnostic clinic given

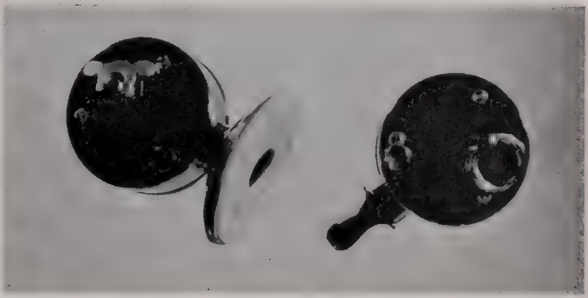

Fig. 6 — The better hearing ear must be "masked" with loud sound in order to accurately evaluate the hearing of a grossly poorer ear — the Barany masker.

to more precise and sophisticated analysis. The quantitation of speech threshold and accuracy for speech itself requires equipment and personnel beyond the range of a general medical examination.

Barany Noise Maker

A gross difference in the hearing of the two ears in a given patient demands one additional test precaution. Significant hearing capacity can be falsely attributed to a severely deafened ear because the patient is unknowingly using the better hearing ear during testing. The skull will carry sound to the better ear with only modest transmission loss. A totally deaf ear will thus be considered to have useful hearing. The general medical evaluator can avoid this pitfall by "masking" out the better ear. The simplest reliable method is by an inexpensive noise-making device applied closely to the good ear — the so called "Barany noise maker" (Figure 6). With the good ear totally preoccupied the examiner can test with words delivered to the handicapped ear in whispered, soft, or loud voice at a distance from arm's length to near contact.

Loss of Cochlear Function

One of the common hearing tragedies of childhood is a unilateral loss of cochlear function as a result of mumps. Unless the opposite ear is "masked out" during testing, a mistaken "modest loss" will be diagnosed and proper concessions for compensatory favorable classroom seating will not be provided. Even worse, purposeless treatment or surgery may be recommended.

In the adult sudden severe or total unilateral loss of hearing with or without tinnitus is a sufficiently common problem to merit general medical awareness and respect. The otoscopic examination will show no abnormality, but voice testing with the better hearing ear masked will demonstrate a gross hearing loss. Temporizing with pointless antibiotic or similar management can dissipate the short-lived reclamation opportunity. Unless aggressive treatment with vascular bed correction (intravenous procaine, heparin, cervical sympathetic block, etc.) is applied vigorously and early, the cochlear deterioration rapidly progresses to irreversibility. Here the general physician contributes tremendously through early recognition of the patient with "sudden deafness."

Meniere's Disease

Meniere's disease is a very common cause of serious sensorineural hypacusis.* It may involve both ears. It originates in the cochlea and for a long time or always it may be a purely cochlear disturbance (Figure 7-a). It causes a sense of fullness in the ear, tinnitus and hearing loss, and is often ignorantly misconceived to be an ordinary auditory tubal closure. The tuning fork, however, will lateralize away from the faulty ear and will be heard better through the canal than when applied to the mastoid process of the affected

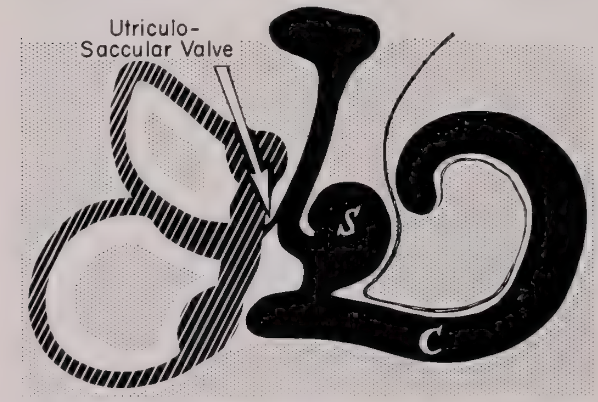

Fig. 7 — (a) Meniere's disease originates in the cochlear segment of the labyrinth and may be confined there with resulting aural pressure, tinnitus, and hearing loss but without vestibular involvement, or

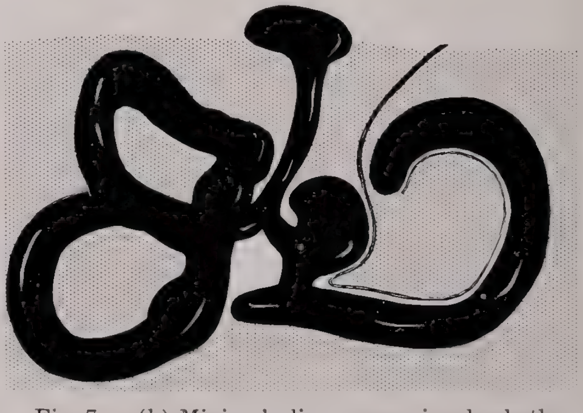

Fig. 7 — (b) Miniere's disease may involve both cochlear and vestibular segments of the labyrinth and result in the better known triad of tinnitus, hearing impairment and episodic vertigo.

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*See Test Your Word Score Page 607.

ear. When episodic vestibular disturbance occurs to round out the symptomatic picture, diagnosis is relatively easy (Figure 7-b).

Meniere's disease is a "stress" disorder. Management with combinations of neural blocking agents such as diphenhydramine and hyoscine, or with intravenous procaine, heparin, or sympathetic block can be effective in controlling the acute catastrophe. Restoration of normal tonus to the endolymphatic system is, however, difficult, and the hearing tends to remain impaired. Much study is being given to the problem. Certainly prophylaxis is dependent on a "stress-free" life. Here the general physician can be the key to good management.

Tinnitus

The patient whose primary complaint is of tinnitus deserves a respectful hearing. Vibratory sound synchronous with the pulse is often indicative of eddying flow in an intra- or extracranial artery. It may be the first sign of a progressive occlusion and, as such, be exceedingly meaningful. Tinnitus arising from the sensorineural elements of the cochlea can be an early sign of systemic, circulatory or metabolic fault. The cochlear neuroepithelium is distressingly sensitive to toxemias of wide diversity. Tinnitus in the absence of obvious visible aural fault demands an exhaustive systemic assessment.

Other Sensorineural Loss

Progressive sensorineural hearing loss is inherent in certain families and becomes evident in the fifth and sixth decades. However, this incidence is far outnumbered by more specific and controllable etiologic sources such as occupational sound injury, systemic disease, and faulty living habits (stress, tobacco, etc.). Here again the general physician has an important function in retarding the progressive deterioration by assuring optimum general well being and giving sympathetic guidance.

All in all there is ample reward for the physician who recognizes the presence and gravity of hearing loss and gives it the dignity of a place in the medical conscience.

President's Letter continued from page 559.

Administration qualified by position to speak with authority and respond with definitive answers.

At a time when the implementation of the Medicare Law is so imminent, this part of the program should be a stimulus for attendance by every Minnesota physician, for by then the regulations under which we will practice should be codified, available for discussion, and subject to criticism, where indicated, by us, the physicians upon whom the program will depend.

Set aside the time now; attend, participate, and inform yourself fully in this departure from the past and this change which confronts us in the future.

R P Buckley M.D.

R. P. Buckley, M.D.
President
Minnesota State Medical Association

Prejudice

Prejudice is a great time-saver. It enables one to form opinions without bothering to get the facts. — Kitchener (Canada) Record

One trouble with birth control is that it can't be made retroactive.

— Herbert Prochnow

Aortoiliac Occlusion*

PATIENTS WITH occlusion of the terminal aorta and iliac arteries are being seen more frequently, perhaps because of increased familiarity with the Leriche syndrome† and recognition that effective treatment for the symptoms is often available. The average ages in the series reported in the literature have ranged from 49 to 55 years, though many authors[1,2,3] have verified that aortoiliac occlusion can occur in men in their thirties. The symptoms are especially disabling in this still vigorous, still working age group and can force an early retirement.

Clinical Data

A series of 40 private patients, 34 males and six females, has been seen by the surgeons at The Duluth Clinic since 1958.

History

Their ages ranged from 36 to 71 years, with symptoms present for as long as ten or twelve years prior to being admitted to the Clinic. Seventeen had previous evidence of generalized cardiovascular disease (Table 1). The serum cholesterol was abnormally high in 16; 37 were known smokers, 15 of whom smoked two or more packs of cigarettes a day.

Symptoms

The median duration of symptoms was one year. Claudication‡ of the calf was almost as common as claudication of the hip and thigh; six patients had noted claudication only in the lower leg. Eight patients had marked ischemia of the legs, although dependent rubor of the feet as well as other skin changes were infrequent. Both femoral pulses were markedly diminished or absent in 32 patients; in eight the femoral pulse was missing in one leg (Table 2).

Diagnostic Studies

Ninety per cent of the patients underwent translumbar aortography, and distal arteriograms were obtained following the single aortic injection. Direct femoral arteriograms were secured in 17 patients, four of whom had bilateral studies. These x-rays showed partial obstruction of the aorta in two patients and complete occlusion in 11. Seven of the aortograms demonstrated that obstruction of the aorta began just below renal artery level. There was complete obstruction of the right iliac artery in 10 patients and partial obstruction in 11. The left common iliac artery was completely occluded in 22 patients and partially occluded in five. Twelve patients had unilateral and three bilateral obstruction of the superficial femoral or popliteal artery, but in all the patients the profunda femoris artery was patent and furnished adequate runoff circulation.

Management and Results

The Nonsurgical Group

Ten patients did not undergo surgery (Table 3); the symptoms were minor in two; two plan to return in the next several

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*Presented before Minnesota Surgical Society in Duluth in 1965.

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†See page 579.

‡See Test Your Word Score Page 607.

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R. H. LA BREE, M.D., F.A.C.S.**
Duluth, Minnesota

months for their surgery; two refused surgery; two underwent exploration, but nothing could be done for technical reasons (one had a horseshoe kidney and the other retroperitoneal fibrosis); and in two the occlusive process was deemed too extensive to be helped.

Sympathectomy Group

In none of the patients did sympathectomy relieve claudication, but it did relieve rest pain in three of the four patients with this symptom. Sympathectomy resulted in dry, warm, and often pinker feet in these patients. It was performed in combination with

TABLE 1

40 Patients with Aortoiliac Occlusion

Medical Data			
Obese	6 Patients	Cigarette smoker	37 Patients
Diabetic	5	(Unknown - 3)	
		(Heavy - 15)	
Serum Cholesterol (32 Patients)		Hypertensive	11
		Angina	3
175-199 mg. %	4 Patients	Myocardial Infarction	3
200-249 mg. %	12		
250-299 mg. %	8		
300-400 mg. %	8		

TABLE 2

40 Patients with Aortoiliac Occlusion

Symptoms		Physical Findings	
Claudication in hip or thigh (19 also had calf claudication)	32	Both femoral pulses missing	10
Claudication in calf only	6	One femoral pulse missing; the other faint	16
Rest pain	7	Both femoral pulses faint	6
Abrupt paralysis of legs	1	One femoral pulse missing; the other present	8
Impotent	7	Abdominal bruit	7
Numbness in foot	8	Dependent rubor of feet	3

endarterectomy in 17 cases and with insertion of a graft in 10 cases.

Endarterectomy

Endarterectomy restored the circulation in ten legs, but four showed evidence of reocclusion of the iliac artery within three years after surgery. In three of the patients who underwent endarterectomy the vessels have remained patent for over five years.

Bypass Graft

Insertion of a bypass prosthetic graft proved to be the most successful technique for relieving aortoiliac occlusion (Figures 1 & 2). Femoral pulses were restored in 16 of 17 legs operated and pedal pulses were restored in 15 of these limbs. The claudication was relieved by the graft in all but one patient; this patient expired following amputation of the limb. Two of the patients who underwent a unilateral grafting operation later redeveloped distal arterial insufficiency, and in one patient this necessitated amputation.

Of the patients who underwent surgery four died, an operative mortality of 13 per cent. Three of these deaths followed unsuccessful endarterectomy or grafting procedures.

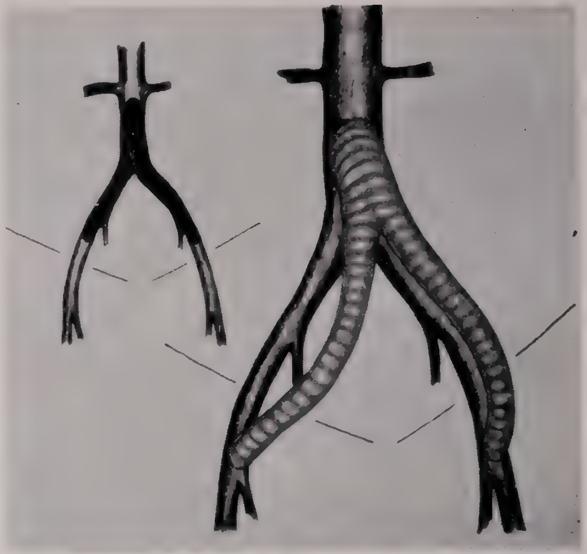

Fig. 1 — Diagram of an extensive aortoiliac occlusion managed by local endarterectomy of the aorta and end-to-side dacron aortofemoral bypass graft.

Report of a Case

A 66-year-old former machinist had complained of increasingly severe intermittent claudication of both buttocks and thighs for two years prior to being seen at The Duluth Clinic. He had noted numbness in the right thigh on prolonged standing or when sitting with his legs crossed. In recent months there had been severe cramping in the thighs and calves after walking one-half block. The cramping disappeared within five minutes if he stood still. His general health had otherwise been excellent and a review of systems elicited no further complaints. He

TABLE 3

40 Patients with Aortoiliac Occlusion

Management		Results	
Nonsurgical	10 Patients	Slow progression 3-5 years	3 Patients
		Stable 3-5 years	3 Patients
Sympathectomy	6	Relief of rest pain 1-7 years	3 Patients
Unilateral	2	Limb amputated 7 years later	1
Bilateral	4	Postoperative death	1
Endarterectomy	14	Pulses restored	10 legs
Aorta	1	Claudication relieved	9 legs
Aorta and one iliac A.	10	Amputated	2 legs
Aorta and both iliac A.	3	Postoperative death	2 Patients
Insertion of prosthetic graft	10	Pulses restored	4 legs
Unilateral	3	Claudication relieved	4 legs
Bilateral with resection	1	Amputated postoperatively patient died	1 leg
		Amputated 8 months later	1 leg
Bilateral with bypass	6	Pulses restored	12 legs
		Claudication relieved	12 legs

had smoked two packs of cigarettes a day for many years.

Examination

Examination revealed a healthy, mildly obese male. The blood pressure was 134/82 and the pulse 84 per minute and regular. The heart was of normal size to percussion. There was a grade II/VI coarse systolic murmur in the aortic region which radiated to the neck. The lungs were clear to auscultation and percussion. Abdominal examination was normal. The aortic pulse could not be felt and no bruit was heard.

The feet were slightly pale, and on elevation marked pallor developed. After the legs were lowered the color return was delayed in both feet. Neither the femoral pulses nor the more distal pulses in the legs could be felt.

Laboratory Studies

The hemoglobin was 15.6 grams per cent and the urinalysis was normal. A serum cholesterol was 238 mg. per cent. The electrocardiogram and chest x-ray were normal. Translumbar aortography showed the abdominal aorta to be completely occluded distal to the origins of the renal arteries which were well delineated. Vague shadows outlined the distal external iliac arteries.

Operative Findings

On July 7, 1965, the patient was taken to surgery and the common femoral arteries were exposed by an incision in each thigh. Direct bilateral femoral arteriograms confirmed that the superficial and deep femoral arteries were patent on each side. The popliteal arteries and their branches were also open. At laparotomy the abdominal aorta distal to the renal arteries was found to be nonpulsatile and firm. A small aneurysm was present in the aorta. Pulsations could not be felt in the fibrotic common and external iliac arteries.

Operative Procedure

Bilateral lumbar sympathectomy was performed. Then the abdominal aorta was transected 1.5 cm. distal to the origin of the renal arteries, and after proximal thromboendarterectomy a good brisk flow of blood was secured from the proximal aorta. During this time the renal arteries were occluded with clamps for four minutes. The aneurysm was excised and the terminal aorta oversewn with 3-0 polyethylene suture. A knit dacron bifurcation graft was then anastomosed end-to-end to the proximal aorta. The limbs of the graft were tunneled beneath each inguinal ligament and anastomosed end-to-side to the common femoral artery of each leg. The procedure is illustrated in Figure 3. After completing the right anastomosis, the right leg was profused with blood during suturing of the left limb of the graft. At the end of the operation there was an excellent flow of blood through the graft with good pulses in the common, superficial and deep femoral arteries. Dorsalis pedis pulses could be felt in both feet. Intravenous infusion of five per cent Mannitol solution was begun just prior to the thromboendarterectomy and was continued throughout the procedure. The patient received one unit of dextran and two units of blood during operation.

Postoperative Course

Mild gross hematuria was noted for the first 24 hours after surgery. At no time was there evidence of decreased renal function. Serial determinations of serum urea nitrogen and creatinine during the postoperative course disclosed normal values. The incisions healed by primary intent, and on the day of discharge from the hospital (July 21) there were strong (grade IV) pulses palpable in each foot. The patient has taken mile-long walks without discomfort.

Follow-up Data

Half of the patients have been followed for at least two and a half years and some

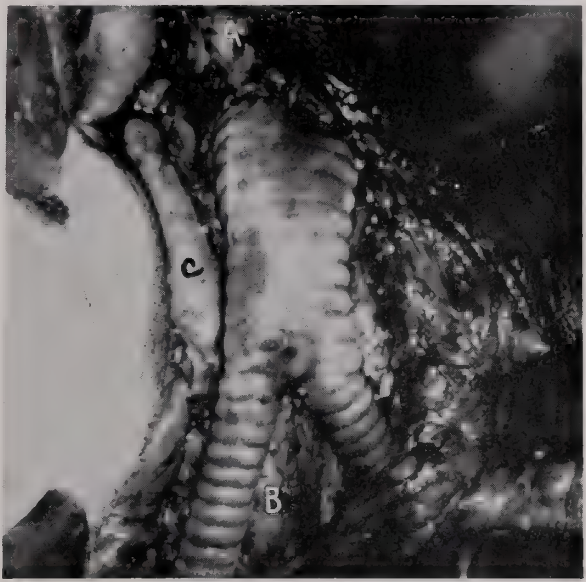

Fig. 2 — Photograph of end-to-side bifurcation aortofemoral bypass graft in place. (A) Aorta. (B) Right iliac artery. (C) Inferior vena cava.

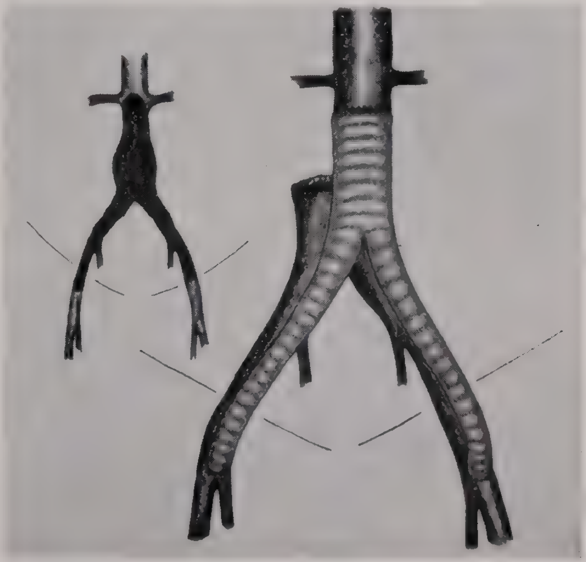

Fig. 3 — Diagram of aortoiliac occlusion with a small aortic aneurysm. Resection of the aneurysm, closure of the distal aorta, and insertion of an end-to-end bifurcation aortofemoral bypass graft were performed.

for over six years (Table 4). There have been 11 late deaths, the great majority of these due to cardiovascular disease. One third of those patients observed for one year or longer have shown progression of the arteriosclerosis with further diminished peripheral circulation. However, 11 patients followed for three to six years have not demonstrated evidence of further vascular occlusion.

Discussion

Friedman[3] has found an increased incidence of hypercholesterolemia in these patients, and this was likewise present in our series. Hypertension was also frequent in the present study. The smoking history of the patients studied would appear to be heavier than in the general population. Hammond,[4] in a study of 31,733 Minnesota males, ages 40 to 89, found that 26.5 per cent had never smoked and 47.5 per cent smoked one to 19 cigarettes a day or had discontinued smoking. Only 26.0 per cent smoked one pack or more of cigarettes a day.

In Szilagi's[5] experience there was evidence of systemic arteriosclerotic disease in one third of the patients with aortoiliac occlusion. It has been stated that 20 per cent of patients can expect a major cardiovascular complication within five years.[1] Nondiabetic patients have a better prognosis.[6] Most studies have shown 15 per cent late deaths; but the mortality has been approximately 50 per cent in patients followed for five to ten years.[7] The results of this study would appear to be in agreement with these figures.

A fairly certain diagnosis of obstruction of the aorta or iliac vessels can be made on clinical symptoms and findings. Translumbar aortography confirms the clinical impression and outlines the extent of the disease. In patients with femoral-popliteal occlusion aortography has on occasion shown a surprising degree of involvement of the iliac arteries as well. If the patient is hypertensive the dye can be injected at a higher level to obtain renal arteriograms. Although some surgeons have abandoned aortography we continue to believe it an aid that allows us to better plan the surgical approach and to proceed with confidence.

The operative mortality for patients undergoing sympathectomy is low. The mortality has also remained low for either endarterectomy or grafting procedures if good arterial flow can be successfully reestablished. Since an open deep femoral artery will insure continued patency, direct arterial surgery is now offered to almost 90 per cent of these patients. In reviewing the cases and x-rays we felt that in four patients in whom reocclusion of the vessels occurred following endarterectomy and in eight patients who underwent sympathectomy alone bypass grafts could have been successfully inserted. On the other hand, correction of coexistent femoral-popliteal obstruction is best deferred until later.[5,6,8,9] In most cases it will not be required, since lower leg ischemia will have been adequately relieved by aortoiliac reconstruction.

Endarterectomy has been used for patients who have a short segmental obstruc-

TABLE 4

40 Patients with Aortoiliac Occlusion

Follow-Up Data
Range - 0 to 7 Years
Average - 2 Years
Median - 2.5 Years

Late Deaths - 11 Patients		Progression of Disease	
Myocardial infarction	7 pts.	Not eligible for study	16 pts.
Cerebrovascular accident	1	Progressive disease	8 pts.
Carcinoma of tongue	1	Condition stable (11 pts. for 3 to 6 years)	16 pts.
Progressive retroperitoneal fibrosis	1		
Unknown cause	1		

tion of the aorta or common iliac artery. Often, however, there is narrowing and fibrosis of the external iliac arteries. Long thromboendarterectomy of the iliofemoral arteries is advocated by Cockett and Maurice,[8] but this type of lesion has not proven easily amenable to endarterectomy in our experience, or in that of others.[1,5,6]

For most patients we feel that the procedure of choice is a bypass bifurcation graft as first suggested by Kunlin[10] and soon thereafter advocated by Linton and DeBakey.[6] The advantages of the graft are its greater ease of insertion as compared to an extensive endarterectomy, the failure of atheroma to develop in the graft itself,[11] and the facility with which the graft can be brought distally to the common femoral artery. Recent results with bifurcation aortofemoral bypass grafts have been gratifying, and we intend to use this method in a higher proportion of cases in the future.

Summary

In forty patients presented the incidence of cigarette smoking was considerably higher than in the general population. Endarterectomy has restored the circulation in a fair proportion of cases, but insertion of a bypass prosthetic graft has been more successful.

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ALDRICH SYNDROME*

This syndrome was first described by Wiskott in 1937, and Aldrich, Steinberg, and Campbell in 1954. Approximately 60 cases have been reported, usually occurring as a sex-linked recessive inheritance pattern and characterized by chronic eczema, thrombocytopenia and recurrent infections. The majority of children affected have died as a result of overwhelming bacterial infection. Giant-cell pneumonia, cytomegalo-virus infection and eczema herpeticum have been described as additional complications. Recently a new dimension has become apparent, with reticuloendothelial malignancy developing during the course of the disease. Clinically, the onset is within the first six months of life with the majority of children dying within five years. Treatment consists of supportive care. Immunologically these children have been shown to have a lack of natural-occurring isoagglutinins, lymphopenia, and inability to manifest delayed hypersensitivity.

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*See page 583.

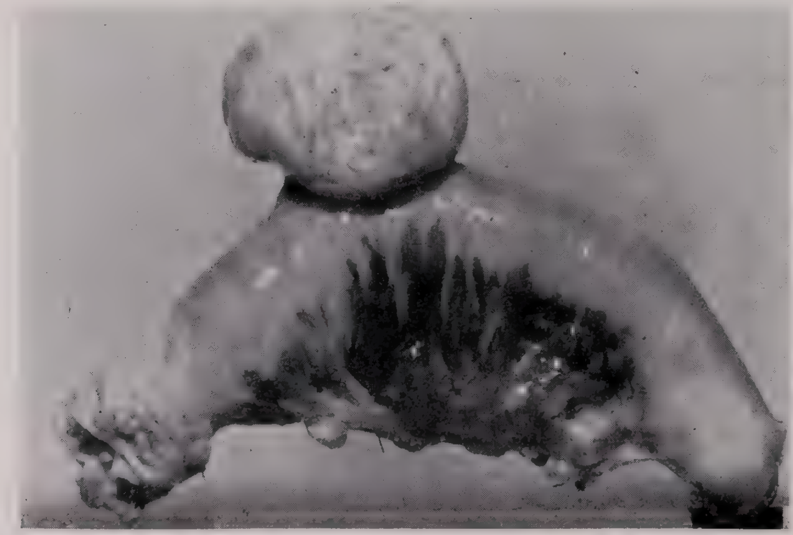
A fat paunch never breeds fine thoughts. — Saint Jerome (345-420 A.D.)

Primary Small

OVER THE PAST 20 years considerable attention has been paid to the problem of tumors of the small bowel. Despite the rarity of these tumors, radiologists and clinicians should be acquainted with the clinical and radiological aspects of this problem, as frequent, unexplained anemias are due to these lesions. Sorlin in 1824 was the first to report a case of small bowel tumor. Good compiled data on 659 tumors of the small intestine, about half of which were benign and half malignant. Sawyer, in 267 cases of complete intestinal obstruction, found that 6.5% were due to small bowel neoplasms. From 1920 to 1960 a total of 650 cases of primary, malignant lesions of the small intestine were reported. According to Good, myomas, adenomas and lipomas are the most common of the benign lesions. Single polyps and hemangiomas are next in frequency. Much less common are aberrant, pancreatic rests, and some systemic diseases which may have tumoral involvement of the small intestine, such as Peutz-Jeagher* and VonRecklinghausen's disease. The most common malignant lesions are carcinoid, adenocarcinoma, lymphoma, leiomyoma and leiomyosarcoma. The correct preoperative clinical diagnosis of a small bowel tumor is rarely made; about 58 of all benign and malignant small bowel tumors are incidentally discovered at operation or necropsy.

Symptoms

Anemia of unexplained origin, partial or complete intestinal obstruction, loss of weight, gastrointestinal bleeding and pal-



Leiomyoma of ileum.

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*See Minnesota Med 48:1468, 1965.

Bowel Tumors

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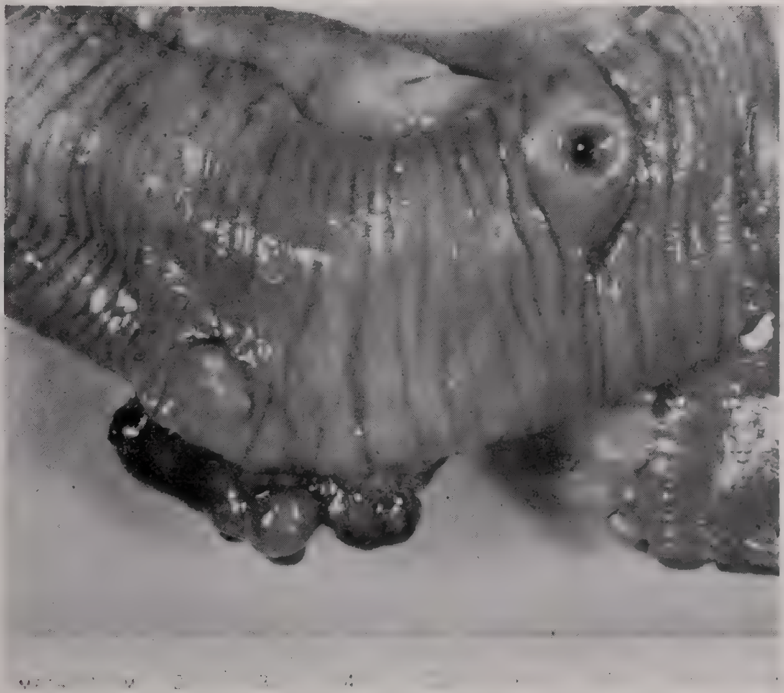
pable abdominal mass are the most common clinical features of small bowel tumors. Less common are diarrhea, weakness, fever and pallor. According to Good, 78% of the patients with symptomatic tumors complained of pain or had signs of partial intestinal obstruction. Sixty-eight per cent of the patients had some loss of weight, more common among patients with symptomatic, malignant tumors (71%) than among those with symptomatic, benign tumors (22%). Southan found that about 50% of the cases had a massive hemorrhage as the initial symptom. This symptom is very common in hemangiomas and adenocarcinomas and also in cases with leiomyomas and leiomyosarcomas, the most severe bleeding occurring with leiomyomas. A mass is palpable in about 20% of benign tumors and in 44% of malignant tumors. Fraser has estimated that approximately 65% of sarcomas and only 29% of carcinomas eventually become palpable. While x-rays of the duodenum and proximal jejunum will give the diagnosis in a high percentage of cases, such diagnosis is seldom possible in the distal segments of the small intestine, where the lesion can sometimes be shown only after a very careful



Leiomyosarcoma of ileum showing umbilication of mucosa, source of bleeding.

fluoroscopic examination. Recently cinefluoroscopy has helped greatly in locating lesions in the jejunum and ileum; however, a negative x-ray examination does not mean that the presence of a neoplasm has been excluded.

The diagnosis of small bowel tumors should be seriously considered in all cases of small bowel obstruction and/or intussusception. Serotonin investigation of the urine should be helpful in some cases. Ulcerations, filling defects and blank spaces are common radiological features in neoplasms of the small bowel.

Observations in this Study

This study is based on 32 cases of primary small bowel tumors seen at two Minneapolis hospitals during the past 10 years. These hospitals operate as private, nonprofit institutions under a joint teaching program and are staffed by a number of general surgeons, all of whom have kindly given permission for the review of their cases, 10 of which were seen by one of the authors. Only clinical material has been considered. All autopsy cases have been excluded (Table 1).

TABLE 1

Histologic Types in 32 Primary Small Bowel Tumors Found at Swedish - St. Barnabas Hospitals (1954-1964)

Malignant	Duodenum	Jejunum	Ileum	Multiple	Total
Carcinoid			8		8
Lymphoma		4	2		6
Carcinoma	2	1	1		4
Leiomyosarcoma	1	1	1		3
Total	3	6	12		21
Benign					
Leiomyoma	2	2	1		5
Hemangioma				2	2
Adenomatous polyp	1				1
Cyst		1			1
Pancreatopic rest	1				1
Neuroma	1				1
Total	5	3	1	2	11

The Histologic Types and Location

In the malignant group of 21 cases, the age range varied between 32 and 80 years. The ratio of women to men varied from five to three in the malignant groups and two to one in the benign series.

Duration of Symptoms Before Surgery

In the benign tumors eight out of 11 were incidental findings and in only three was the

TABLE 2

Clinical Features in 32 Cases of Primary Small Bowel Tumor Found at Swedish - St. Barnabas Hospitals (1954-1964)

Benign Tumors	Cases	Asymptomatic	Anemia	Melena	Pain	Obstruction	Mass	Weight loss	Incidentally	Clinically	X-ray
Leiomyoma	5	1	2	2		2	2	2	3	1	2
Hemangioma	2	2	2					2	2		
Miscellaneous	4	3			1				3	1	1
Total	11	4	4	4	1	2	2	4	8	2	3
Malignant Tumors											
Carcinoid	8	1			3	4	2	2	7	1	
Adenocarcinoma	4		3	2	1	2		3	2	2	3
Malignant Lymphoma	6		4	3	3	2	3	5	3	2	3
Leiomyosarcoma	3		2	2	1		1	1	2		2
Total	21	1	9	7	8	8	6	11	14	5	8

diagnosis suspected. It is not possible to make an estimate of the duration of symptoms in this group. Of the malignant tumors we found the average duration of symptoms to be from five years for leiomyosarcomas to two weeks for adenocarcinomas.

Symptoms

Signs of gastrointestinal bleeding were evident in the benign tumors though others were asymptomatic. In one patient with an ectopic pancreatic tumor of the duodenum the lesion was suspected by history of epigastric pain and duodenal filling defect by x-rays.

Of the malignant tumors, anemia and melena were the most commonly observed symptoms. Pain, a palpable mass, weight loss and intestinal obstruction were occasional, though not constant symptoms (Tables 2 and 3).

Comments

Clinicians should be alert to the clinical pattern and the radiologist should be aware of the roentgen abnormalities which may be produced by these tumors. In our series the diagnosis was made by the radiologist on the basis of a filling defect of ulceration in 11 cases (34%) (Table 4). In addition to these 11 cases the x-rays gave the diagnosis of small bowel obstruction in seven cases. In this way 18 of our cases were directly or indirectly diagnosed by x-ray, a fact which points up how useful a careful radiological study may be in this type of lesion.

TABLE 4

Tumors Diagnosed By X-Rays

Benign	Duodenum	Jejunum	Ileum
Pancreatic ectopic rests	1		
Leiomyoma	1	1	
Total	2	1	
Malignant			
Lymphoma		2	
Adenocarcinoma	3		
Leiomyosarcoma	1	2	
Total	4	4	

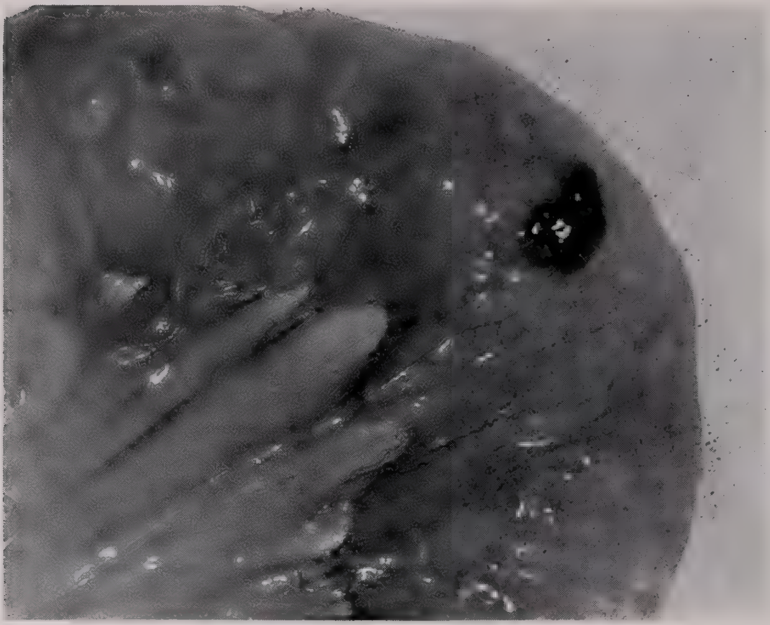
In our series the most common small bowel tumor was the carcinoid, asymptomatic in 65% of the cases; whereas 47% of the adenocarcinomas were symptomatic. The carcinoid may be associated with multivalvular involvement of the heart, and if it is a functioning tumor the urinary determination of five hydroxyindol-acetic acid has been found to be the best test for its diagnosis.

Wide resection of the segment of bowel

TABLE 3

Results of 21 Primary Malignant Small Bowel Tumors at Swedish - St. Barnabas Hospitals (1954-1964)

Type	Surviving	Died	Cause of Death
Carcinoid (8)	3 yrs. 10 mo. 6 yrs. 3 yrs. 8 mo. 13 mo. 9 mo. Reop. acute bowel obstr. No metastasis	6 mo. 9th day	Fecal fistula Fecal fistula
Adenocarcinoma (4)	9 mo. 10 yrs.	34th day 14th day	Cardiac failure Peritonitis & BP
Malignant lymphoma (6)	5 yrs. 9 mo. 16 mo. Mult. met. 1 yr. Ventral hernia repair	9 mo. 8 yrs. 5th day	Unknown Unknown Pulmonary embolism
Leiomyosarcoma (3)	5 yrs.	2 yrs. 7 mo. 2 mo.	Mult. met. Mult. met. & sm. bowel obst.



Haemangioma of jejunum.

involved with its mesentery is the accepted treatment for all malignant lesions. For lymphosarcomas the resection should be followed by roentgen therapy. The prognosis of malignant tumors of the small intestine is relatively poor. None of the patients with adenocarcinoma, who had metastases at operation, survived more than 12 months.

Conclusions

1. Of the 21 malignant tumors, eight were carcinoid or argentaffinomas, six lymphosarcomas, four carcinomas, and three leiomyosarcomas.
2. Of the benign tumors the most common were the leiomyoma and the hemangioma.
3. The most common clinical features were gastrointestinal bleeding, obstruction, abdominal pain and a palpable mass.
4. X-rays provided the diagnosis in 11 patients or 34%. X-ray examination is of paramount importance in the diagnosis of primary small bowel tumors.
5. The surgical excision of malignant lesions is the treatment of choice.
6. The long-term results are excellent in benign tumors but poor in malignant lesions.

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11-26 May be secured from the author or the reprints.

Give me a lever long enough, and a fulcrum strong enough, and singlehanded I can move the earth. — Archimedes

Lupus Erythematosus

Presenting as An Acute Abdomen

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ALTHOUGH ABDOMINAL pain is a frequent symptom in patients suffering from systemic lupus erythematosus, it is usually overshadowed by other more significant features of the disease.[1-3] The occurrence of acute abdominal pain simulating a surgical emergency is relatively rare and usually presents a difficult diagnostic problem in a patient known to have systemic lupus erythematosus. It is even more uncommon to find acute abdominal pain requiring surgical exploration as the presenting manifestation. The purpose of this paper is to report such a case and the evidence that ultimately led to the diagnosis.

Report of Case

A 20-year-old white man was brought to the hospital emergency room because of severe abdominal pain. He had been in good health until four weeks prior to admission, at which time he had noted generalized malaise, fatigue, and the passage of black stools. Anemia had been noted by his physician, and parenteral as well as oral iron therapy had been started. Twenty-four hours prior to admission, the patient had noted anorexia and nausea, followed shortly by increasingly severe cramps with mid-abdominal and right lower quadrant pain. No fever, emesis, or dysuria had been noted.

The physical examination revealed a well-developed, well-nourished man in moderate distress from abdominal pain. The pulse rate was 72 per minute, the temperature, 98.0° F., and the blood pressure, 118/68 mm. of mercury. There was generalized abdominal guarding, right lower quadrant tenderness, rebound tenderness, and a positive iliopsoas sign. The bowel sounds were decreased. Rectal examination revealed marked tenderness on the right side.

The hemoglobin concentration was 9.2 gm. per 100 ml. of blood and the leukocyte count was 3200 cells per cubic mm. with a differential count of 15 per cent lymphocytes, 9 per cent monocytes, 75 per cent neutrophils, and 1 per cent eosinophils. The urinalysis revealed grade 2 proteinuria, grade 1 granular casts, grade 1 microhematuria, and grade 1 pyuria.† The thoracic roentgenogram was normal.

Surgical exploration was advised because of the severity of the symptoms and the signs of peritoneal irritation. Of the several possible diagnoses, Meckel's diverticulitis was most strongly suspected. On opening the peritoneum, the surgeon noted an edematous, inflamed omentum. Three feet proximal to the ileocecal valve, an 18-inch length of ileum was thickened, edematous. and reddened. The mesenteric lymph nodes were enlarged and hyperplastic. The spleen was slightly enlarged but otherwise appeared to be normal; also the cecum, terminal ileum, and appendix were normal. Approximately two feet of the ileum with its mesentery was resected and an appendectomy performed; the surgical specimen is shown in the figure. Microscopic examination revealed an inflammatory infiltrate of the muscularis and edema involving the mucosa of the middle half of the resected specimen. This was interpreted as an early stage of regional enteritis. There was no evidence of arteritis.

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**Section of Medicine, Mayo Clinic and Mayo Foundation.

†Graded on the basis of 1 to 4.

An adjacent lymph node showed only chronic inflammatory changes.

The patient received 500 ml. of whole blood at operation and 1000 ml. later. The blood was difficult to cross match, which suggested the possibility of a protein abnormality. Electrophoresis of the serum proteins gave the following distribution: albumin, 2.32 gm.; alpha$_1$-globulin, 0.48 gm.; alpha$_2$-globulin, 1.01 gm.; beta-globulin, 0.65 gm.; and gamma-globulin, 2.14 gm. per 100 ml. of serum. The possibility of lupus erythematosus was entertained, but the patient refused further investigation and was dismissed on the eleventh postoperative day.

He was next seen six and a half weeks later, at which time he stressed that he felt perfectly well; however, on further questioning, he admitted to some arthralgia in the wrists and knees and occasional epistaxis. The physical examination was entirely normal. The hemoglobin concentration was still low (9.5 gm. per 100 ml.), and the leukocyte count was 3200 with 35.5 per cent lymphocytes, 5.0 per cent monocytes, 55.5 per cent neutrophils, and 4.0 per cent eosinophils. The erythrocyte sedimentation rate was 122 mm. in one hour (Westergren). The reticulocyte value was 1.8 per cent and the platelet count 108,000 per cubic mm. The peripheral blood smear showed moderate anisocytosis and marked rouleau formation. Urinalysis revealed grade 3 proteinuria, erythrocyte casts, waxy, hyaline and granular casts, and leukocyte casts, as well as microhematuria and pyuria. Electrophoresis of the serum proteins gave a distribution similar to that obtained earlier. The blood urea concentration was 50 mg. per 100 ml. The Venereal Disease Research Laboratory and Kahn tests were weakly reactive, and examination for cryoglobulins was positive. The lupus erythematosus clot test was negative on two occasions. It was noted at this time that there was difficulty getting the specimens to clot, and an active circulating anticoagulant of the type usually associated with systemic lupus erythematosus was demonstrated. Examination of the bone marrow showed it to be hypercellular with prominent capillaries with swollen endothelial cells and thickened walls.

Despite the negative lupus erythematosus clot test, it was thought that the patient had a collagen disease like systemic lupus erythematosus.

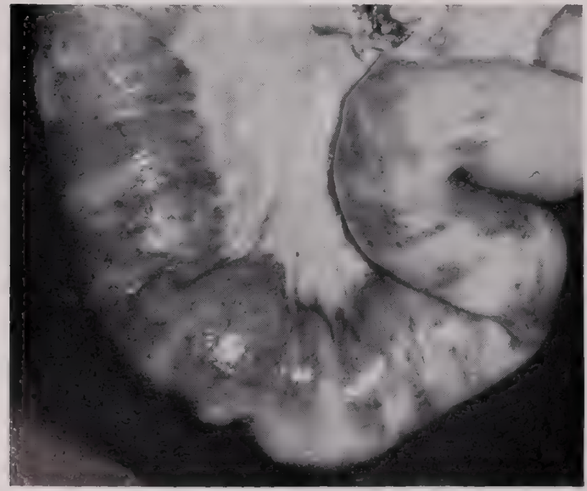

Figure. — Surgical specimen consisting of approximately 2 feet of ileum with its mesentery.

Comment

Severe abdominal symptoms simulating an acute surgical condition are rare in systemic lupus erythematosus. Pollak and co-workers in 1958[4] reviewed 14 such cases and in only two of them was the diagnosis of systemic lupus erythematosus not obvious prior to the onset of abdominal symptoms. Four of the patients presented the clinical picture of acute pancreatitis, with confirmatory laboratory results for this diagnosis in two of the patients. Necropsy studies showed evidence of involvement of the arteries around the pancreas but no actual pancreatic necrosis. The remaining 10 patients presented primarily with nausea, vomiting, fever, and tachycardia. The abdominal pain was dull and occupied either the entire abdomen or the lower half. Abdominal distention was present in nine of the 10 cases, abdominal tenderness was present in every case, and rebound tenderness was striking in seven of the cases. Surgical exploration in these seven cases revealed hemorrhagic edema of the small bowel wall as well as serosanguineous peritoneal fluid. Half of the patients were anemic prior to operation; more than half had leukopenia; and the majority had abnormal urinary sediment.

The diagnostic possibilities in any young patient with acute abdominal pain and anemia include hemorrhagic Meckel's diverticulitis, a hemolytic process, regional enteritis, and the collagen diseases. Inflammation of Meckel's diverticulum causing hemorrhage and peridiverticulitis is rare and is usually associated with leukocytosis. The leukocyte count is similarly increased in hemolytic states with the exception of paroxysmal nocturnal hemoglobinuria. Regional enteritis presenting as an acute abdominal situation is usually accompanied by systemic symptoms and either a normal or an increased leukocyte count. Polyarteritis nodosa should be considered, although here again there is usually leukocytosis. When the combination of leukopenia, anemia, and an abnormal urinary sediment is found in a young patient with abdominal pain, it should suggest the diagnosis of systemic lupus erythematosus. A circulating anticoagulant[5] is found in a number of cases of systemic lupus erythematosus and is most suggestive of this diagnosis. Some of these patients have a negative lupus erythematosus clot test. As the lupus erythematosus phenomenon is intimately related to coagulation, the inhibition of coagulation by a circulating anticoagulant may make this phenomenon difficult to demonstrate. It has been our experience, as in this case, that there has not usually been an associated hemorrhagic tendency; in fact some patients have had a paradoxical thrombosing tendency.[6]

Summary

A case is presented of a 20-year-old man with acute abdominal pain, anemia, leukopenia, and abnormal urinary constituents. A localized area of nonspecific ileitis was found at operation. The presence of a circulating anticoagulant, abnormal serum proteins, and cryoglobulins in addition to positive serologic reactions for syphilis supported the diagnosis of a collagen disease such as systemic lupus erythematosus, despite two negative lupus erythematosus clot tests. It is emphasized that, when leukopenia and anemia are found in association with an acute abdominal condition, lupus erythematosus is a most likely cause even in the absence of associated signs and symptoms of systemic disease.

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LERICHE'S SYNDROME*

This syndrome is characterized by chronic atheromatous or thrombotic occlusion of the abdominal aorta above the bifurcation of the iliac vessels. It is associated with pallor of the feet, cold extremities, cramps in the calves, claudication of the buttocks, hips, thighs, and legs, inability to maintain an erection, and finally impotence.

The condition usually occurs insidiously, though it may develop suddenly from thrombo-embolism. If occlusion is marked or complete, surgical resection of the vessels and appropriate transplant is the procedure of choice.

Durham, Robert H. — Encyclopedia of Medical Syndromes
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*See Aortoiliac Occlusion, page 566.

The Penalty of Overweight

Obesity has a definite and deleterious effect upon the liver, and the most significant relationship seems to be the duration rather than the degree of obesity. — Cyril M. MacBryde, M.D., Signs & Symptoms Lippincott Co.

All candidates have two hats in their wardrobes; one to toss into the ring and another to talk through. — North Adams Herald

Salmonella Pullorum Septicemia

SALMONELLA PULLORUM is found very frequently in chickens and has a wide zoological distribution. Human infection is surprisingly rare, with only a few cases of its isolation reported.[1,2,3,4,5,6,7] No human fatalities have been previously reported.

The purpose of this paper is to present the case history, pathological and epidemiological studies of a child who died as a result of *S. pullorum* septicemia complicating granulomatous disease of childhood.‡ The source of the infection was apparently raw eggs.

Case Report

A two-and-one-half-year-old Caucasian male was born at the University of Minnesota Hospitals of a full-term pregnancy and normal delivery. The mother's pregnancy was complicated by fever in the third month of gestation, and her Mantoux test converted strongly positive. She was begun on isoniazid and pyridoxine therapy and continued throughout her pregnancy. Her chest x-rays have always been negative and she has remained in good health.

The patient was considered well until two months of age when he developed fever, lethargy, and a severe diaper rash. At this time, his liver was enlarged 4 cm. below the right costal margin and generalized adenopathy was present. A large hard mass developed in the right cervical area, and a biopsy was taken and interpreted as chronic and acute inflammation. The cultures of the biopsy specimen yielded penicillin-sensitive *Streptococcus faecalis.*

At eight months of age he was gaining weight and developing normally. He then developed a generalized maculopapular rash and a 100.4 degree fever. Laboratory studies at this time revealed a hemoglobin of 9.5 gm.%, and sedimentation rate of 76 mm. per hour. Skin tests including fungal and tuberculin antigens were negative. Skin scrapings from the intertriginous areas showed budding yeast forms typical of monilia and he was placed on oral and topical mycostatin. Oral ferrous sulfate was administered and his hemoglobin rose to 12 gm.% after two weeks.

Progress Report

During the next fifteen months a persistent seborrheic dermatitis of the scalp was present. His spleen remained 2 cm. below the left costal margin and the liver 3 cm. below the right costal margin. At two years of age he developed a temperature of 100.6 degrees rectally and again was admitted for evaluation of enlarged cervical lymph nodes. Skin tests with atypical mycobacterial and triple fungal antigens were all negative. A repeat lymph node biopsy was performed of a right posterior auricular node, cultures of which were negative for bacteria, fungi and acid-fast bacilli. Histologic interpretation was hyperplasia secondary to chronic cutaneous infection and no granulomata were detected. Laboratory studies revealed a 7.2 gm.% hemoglobin, 9,000 white count with 25% neutrophils, 65% lymphocytes, 5% eosinophils and 2% plasma cells. A bone marrow examination was consistent with an iron deficiency anemia. Cultures of the nose, throat and bone marrow were negative for bacterial, fungal, and acid-fast organisms. He was discharged

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*From the University of Minnesota Medical School, Minneapolis, Minnesota, and the Communicable Disease Center, Public Health Service, U. S. Department of Health, Education and Welfare.

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†At the time this paper was prepared, Dr. Williams was Epidemic Intelligence Service Officer (CDC), assigned to the Minnesota Department of Health, Minneapolis, Minnesota. Presently he is an instructor at Tulane University School of Medicine, New Orleans.

‡See page 595.

*A Bizarre Terminal Event in a Case of Granulomatous Disease of Childhood**

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on oral ferrous sulfate, to which he responded.

Two months later he was admitted for a severe eczematoid rash of the face. A skin biopsy was interpreted as hyperkeratosis with papillomatosis of the epidermis and perivascular round cell infiltrate. A liver needle biopsy was histologically normal. Liver function studies revealed a serum glutamic oxaloacetic transaminase of 32 pyruvate units, serum glutamic pyruvic transaminase of 34 pyruvate units and 0% bromsulphalein retention. Serum electrophoresis revealed total proteins of 7.3 gm.% with 4 gm.% albumin and 3.3 gm.% globulin (0.4 gm.% Alpha 1, 0.7 gm.% Alpha 2, 0.95 gm.% Beta and 1.4 gm.% Gamma). An inflammatory cycle, leukocyte migration test and surface phagocytosis of pneumococci were normal.

Terminal Illness

Following his discharge from the hospital the mother began the feeding of raw eggs in an attempt to "build him up physically." At two and one-half years of age he became acutely ill with a temperature of 103.2 degrees. His spleen was down 8 cm. below the left costal margin; the liver was down 6 cm. below the right costal margin. Laboratory work showed a hemoglobin of 10.0 mg.%; white count was 4,550 with 46% neutrophils, 52% lymphocytes and 2% monocytes. High fever persisted and three blood cultures were drawn. One day later the blood culture reports revealed gram-negative rods, and on this basis intravenous chloramphenicol (150 mg./Kg./day) and penicillin (600,000 units q.i.d.) were administered. Twenty-four hours later his temperature dropped from 103 degrees to 92.5 degrees. Bloody emesis occurred, and a prothrombin time was 50.3 seconds (control 11.3 seconds.) His hemoglobin continued to drop and he died in shock the same day. No other drugs were given during this time and no further laboratory tests were performed. While he was in shock, his liver was rapidly enlarging and quite tender. His death was felt to be the result of both septicemia and acute blood loss.

Blood Culture Studies

The three blood cultures yielded *Salmonella pullorum* in both the broth and pour plates which were sensitive to chloramphenicol and tetracycline. Four stool cultures were negative for salmonellae. Agglutinin titers were 1:80 and 1:60 for *Salmonella typhi* and *Salmonella paratyphi B* respectively. Agglutination tests on the mother and the one-year-old male sibling were negative; however, the father showed no titer for *S. paratyphi B* and positive 1:160 for *S. typhi*. Stool cultures of the mother, father and sibling yielded no *Salmonella*.

Pathology

At autopsy he was a normally developed and well-nourished child. The liver weighed 740 gm. (normal for age — 400 gm.), and there was yellow mottling throughout the parenchyma. The spleen weighed 222 gm. (normal for age — 35 gm.), and on cut section the parenchyma was black, red and hard with a glassy shine. The lungs were wet and engorged throughout. The tracheobronchial lymph nodes were enlarged and firm.

The esophagus possessed a brownish, shaggy mucosal surface. There were numerous ulcerations of the stomach, epiglottis, and vocal cords.

Microscopically there was extensive diffuse necrosis and focal necrosis of the liver, spleen, lymph nodes, bone marrow and Peyer's patches. In association with the areas of focal necrosis, there was moderate monocytic infiltration without leukocytic infiltration. The liver contained nonspecific granulomas, characterized by caseous centers surrounded by a rim of dense fibrous connective tissue containing lymphocytes and plasma cells. One of the tracheobronchial lymph nodes also revealed several small, hyalinized, and fibrotic granulomas which contained several giant cells. The lungs had areas of necrosis, occasional granulomas with giant cells and a chronic confluent pneumonitis. A few pigmented, lipid histiocytes were present in the lungs.

Acid-fast stains and fungal stains revealed no organisms other than hyphael forms of *Candida albicans* in the lungs.

Post-mortem bacteriologic studies detected *S. pullorum* in the splenic tissue and blood. *C. albicans* were isolated from the mouth, skin, adrenals, lung and spleen. There were no other fungal or acid-fast organisms recovered. Viral isolation using human amnion, monkey kidney and Hela cells yielded no virus in the stool, liver, spleen or lung.

Epidemiological Investigation

The mother reported that shortly after this child's birth, she had heard from a physician that the infant's feedings could be "fortified" with raw eggs. She stated further that when the child did not eat well, he was often given egg yolk in his milk. The patient's maternal grandfather owned a feed mill in South St. Paul and he obtained eggs for the families from one of his feed customers (Farm L). The patient's family (four members) consumed about four dozen eggs a week. The patient and his sibling were reported to receive on occasion four raw egg yolks a day. The use of this supplement was accelerated in the five months preceding the patient's death.

An investigation was made of Farm L in October, 1963, where 300 hens were in production. The hens originated from two hatcheries that had had negative pullorum check tests for two years. The birds were housed in the lower level of an old but sound barn and were kept in at night and yarded in the daytime when weather permitted.

The pullets were fed a commercial chick starter ration which contained two animal origin products, meat and bone scrap, and fish meal in proportions that are a trade secret. The producing birds were fed a commercial egg-laying mash. The only animal origin ingredients in this ration were meat and bone scrap and preserved animal fat. Neither of these feeds was medicated with antibiotics.

On November 1, 1963, the farmer permitted testing of 22 of the older hens. The stained-antigen, rapid, whole blood test (plate agglutination test) was used.[8] Ten of the hen bloods were agglutinin-positive (45.5%). Five of these reactor hens were purchased for bacterial isolation. *S. pullorum* was isolated from the ovaries of all five hens. The identification of this serotype was confirmed in the Enteric Laboratory, Communicable Disease Center, U.S. Public Health Service, Atlanta, Georgia, according to the methods of Ewing and Edwards.[9]

The eggs produced on this farm were used by the immediate family and close relatives and sold to drive-in customers only. The wife of Farmer L stated repeatedly that no family members or relatives had been ill, and therefore she was sure that their eggs were not the source of the patient's infection. Due to her hostility no one else was cultured for the presence of salmonellae, and a customer list could not be obtained. No *S. pullorum* isolates have been made in the Division of Laboratories, Minnesota Department of Health, since the death of this patient; therefore, no further cases have been traced to this source. No eggs were cultured and no environmental specimens were taken from the barnyard.

Case Discussion

This two-and-one-half-year-old male had numerous infections during his life, which terminated as the result of *S. pullorum* septicemia. The underlying cause of his recurrent infections, hepatosplenomegaly, cervical adenopathy and eczematoid rash was not determined but his clinical and laboratory findings were most consistent with the syndrome described by Berendes, Bridges, and Good.[10,11] A recent review of this subject by Carson et al.[12] summarizes the findings of this form of granulomatosis. This case probably represents a sporadic form of the disease, as there is no other family member known to be affected. It is of interest that in the paper by Carson et al. four of thirteen cases had *Salmonella* isolates out of which one was septicemic with *S. typhimurium*.[12]

Histiocytosis X, Aldrich's Syndrome,* sarcoidosis and dysgammaglobulinemia were also considered but not documented. The illness of the mother during pregnancy was suggestive of tuberculosis or fungal disease, but repeated attempts to isolate these organisms were unsuccessful. No cases of granulomatous disease in the offspring of mothers receiving either isoniazid or pyridoxine have been reported.

The question may be raised as to whether this child's entire disease process could have been the result of chronic *S. pullorum* infection. This hypothesis seems untenable since many cultures of different sites were taken throughout his course and *S. pullorum* was not encountered until his final episode. The history of increased consumption of raw eggs in the five months preceding death implies that a larger number of *S. pullorum* organisms were available as an infecting dose; also no granulomas have been reported with any type of *Salmonella* infection.

The granulomas found at autopsy in lymph nodes, liver and lung are those described by Berendes et al.[10,11] and by Carson et al.[12] (Figure 1). Giant cells were encountered in the lungs and were apparently related to fungal infection.

Superimposed upon the pathology of the granulomatous disease is that of the salmonellosis. The focal necrosis and monocytic infiltration of the liver, spleen, lymph nodes, Peyer's patches and bone marrow are characteristic of *Salmonella* septicemic infection. The monocytic infiltration with the lack of leukocytic response was striking in the areas of focal necrosis and has been described in typhoid fever.[13] The enlarged liver with yellow mottling and the glossy red-black parenchyma of the spleen are also classically seen in fatal cases of *Salmonella*.[13,14]

This case is primarily important as it relates to the problem of human infection with *S. pullorum*. The possible deleterious effects of the feeding of raw eggs, under-cooked eggs or dried egg powders to humans who are more susceptible to infection either by age or underlying disease processes warrant some further review of this problem.

Most isolations of *Salmonella pullorum* are made from chickens and turkeys. It has also been isolated from other birds, occasionally from animals, and rarely from man. The organism is carried in the ovaries of the hen, its natural host, asymptomatically. Some of the eggs laid by the hens will be infected and chicks hatched from the infected eggs will become carriers.[15]

Investigations of the occurrence of salmonellae in market eggs indicate their presence is rare.[16,17,18] *S. pullorum* has been found in eggs marketed in the United States, but in small numbers.[19,20,21] Dried egg

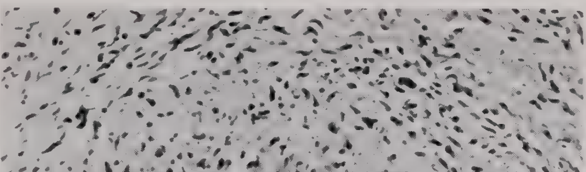

Fig. 1 — Photomicrograph of granuloma of the liver showing caseous center surrounded by a zone of fibrous tissue with deep staining nuclei and plasma cells. [x40]

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*See page 571.

powder, on the other hand, was found by Soloway et al.[22] to contain 11% *S. pullorum* isolates in 5,198 samples of dried egg.

Salmonella pullorum and *gallinarum* are known to have a high degree of specificity for an avian species, especially chickens.[20,21] They have been considered by some to be nonpathogenic for man.[25,26] However, there are reported isolations of these serotypes from man. Seventy-one reported instances of human *S. pullorum* infection have been reported in this country.[1-7] Three reports have dealt with outbreaks of gastroenteritis.[2,6,7] The source of the infections was apparently raw eggs in foodstuffs and eggnog. The remainder of the cultures have been found in sporadic cases of diarrheal disease and one culture has been isolated from a healthy carrier.[1]

Neither septicemia nor death from *S. pullorum* has been previously reported. Saphra,[27] in studying 7,779 cases of salmonellosis between 1939-1955, of which 318 were fatal, reported no cases of *S. pullorum* infection.

Salmonellae are most often isolated from children under the age of five.[26,28] Children in this age group are apparently more susceptible to infection, although this may be allied to increased parental concern which leads them to seek medical attention and subsequent diagnosis.

What the relationship is between the dosage of *Salmonella* organisms and disease is not definitely known. Recent studies have shown that a much greater dose of *S. pullorum* is needed to cause disease in man than several other serotypes tested.[30,31,32] In normal adult prison volunteers previously immunized against typhoid, the disease-producing dose of *S. pullorum* ranged from 1.28×10^9 to 16.0×10^9 organisms,[24] whereas the dose of five other *Salmonella* serotypes were in the range from 1.25×10^5 to 4.45×10^7.[28,29]

What dose our patient was receiving is not known. The number of organisms could have been very low or absent at times. On other occasions, it is conceivable that the dose may have been high; if the entire contents of a bottle were not consumed, it remained at room temperature for a time, and then was added to and/or warmed again prior to consumption. There was no medical history of typhoid immunization and the medical history indicates that this child possessed an impaired resistance to infection because of the underlying pathophysiological condition in addition to his young age.

The chickens may have been infected from three possible sources: the hatchery, the farm environment, or the feed, as all are known to be the origin of avian salmonellosis. As the chickens came from a "clean" hatchery, this seems an unlikely source. While numerous salmonellae have been recovered from animal feeds or ingredients, *S. pullorum* was not isolated from 3,459 samples examined in three recent investigations.[33,34,35]

Summary and Conclusions

A case report of *Salmonella pullorum* septicemia as a terminal event is presented, apparently acquired from the consumption of raw eggs. The clinical course and pathological findings demonstrate an underlying granulomatous disease similar to that described by Berendes, Bridges, and Good.[10,11]

The pathology related to the salmonellosis was diffuse focal necrosis and monocytic infiltration of the liver, spleen, lymph nodes, Peyer's patches and bone marrow. The presence of granulomas in the liver, lung and lymph nodes is related to the patient's underlying granulomatous disease process, and determination of their etiology was unsuccessful.

The epidemiological study showed this child was receiving eggs from a flock heavily infected with *S. pullorum*. This points out the need to take great care in the feeding of raw eggs, under-cooked eggs or dried egg products to humans known to be more susceptible to infection, until such time as these are known to be free of salmonellae. It also emphasizes the need to further control zoonotic disease* in its animal and avian reservoirs.

Acknowledgment

We wish to thank Dr. Barbara Burke for making the pathological material available; Dr. James Daw-

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*See Test Your Word Score Page 607.

son for his encouragement and review of the pathological material; and Dr. B. S. Pomeroy for performing agglutination tests and the isolation of *Salmonella pullorum* from infected hens.

Reprints may be secured from Tulane University School of Medicine, 1430 Tulane Avenue, New Orleans, La., or from the University of Minnesota, Department of Pediatrics.

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8-35 May be secured from the author or the reprints.

IT'S THE LAW

Testimony of Consultant Specialist Need Not Be Corroborated by Referring Physician

Under the rule that a physician consulted for treatment, rather than for examination only, may testify as to a patient's subjective symptoms and his conclusions based on those symptoms, the Wisconsin Supreme Court held that a specialist was a doctor consulted for purposes of "treatment," even though the specialist did not prescribe any treatments to the patient directly.

The patient, injured in an automobile accident, brought suit for personal injuries. After the accident, he had consulted his physician for difficulties with his back and neck. When the patient continued to experience such difficulties, despite treatment by his physician, the physician referred him to a specialist in orthopedics for diagnosis. The specialist examined him, took X-rays, and made a report to the physician. A few months later, the physician sent the patient to the specialist again. Treatment was prescribed directly by the physician, who saw the patient frequently.

At the trial, the specialist testified as to his opinion concerning the patient's injuries, based on his examination and X-rays, and also on the medical history and subjective complaints which the patient communicated to him. The patient's own physician did not testify. The trial court concluded that the specialist's testimony was legally insufficient unless corroborated by the physician. Objection to the specialist's testimony had been made on the ground that, since he was an examining doctor, not a treating doctor, he could not testify on subjective matters.

In overruling the trial court's conclusion, the State Supreme Court said that there was no evidence that the patient had consulted the specialist for the purpose of obtaining testimony for the trial. However, even if this had been one purpose of the consultation, it would not have barred the specialist's testimony, since the consultation had been made for "bona fide purpose of treatment." Obtaining a specialist's diagnosis to aid a physician in treatment is a "bona fide purpose of treatment," the court concluded.

Felkl v. Classified Risk Insurance Corp., 129 N.W.2d 222 (Wis., June 30, 1964)

*Papyrus Ebers**

Constipation and Diarrhea

A glance at the Papyrus Ebers dispels once for all any idea that Constipation is a scourge of the modern world brought about by modern conditions of living and eating. For page after page from the very beginning of the papyrus the Scribe sets down purgative after purgative . . . Castor Oil figures in not a few of them; unfortunately for the patients, in only one prescription is it the sole ingredient:

Berries-of-the-Castor-oil-tree
Chew and swallow down with Beer in order to clear out all that is in the body.

But they are not all as simple as that; nor as effective, one may venture to add.

Leaves-of-the-Castor-oil-plant	1/4
Dates-of-the-Male-Palm	5/6
Cyperus-grass	1/16
Stalk-of-the-Poppy-plant	1/16
Coriander	1/16
Cold Beer	1/2

Keep moist, strain, and take for four days.

Another remedy for Constipation which not only claims to act as a purgative but drives out all the diseases in the body, smacks more of a dawn-of-history cocktail than a purgative. It consists of Half-an-Onion mixed in Froth-of-Beer, and is further described as 'A Delightful Remedy Against Death.' The remedy still persists in the shape of the 'life-saver' dispensed at the public bar, but the ingredients are no longer the same and its purgative action has long since disappeared.

The remedies for Constipation are appropriately followed by a succession of remedies 'to stop the diarrhoea.' As the following examples show their employment was purely empirical:

Green Onions	1/8
Freshly-cooked-Gruel	1/8
Oil and Honey	1/4
Wax	1/16
Water	1/3 dena.

Cook and take for four days.

Figs	1/8
Grapes	1/8
Bread-dough	1/32
pit-corn	1/32
Fresh Lead-earth	1/64
Onions	1/32
Elderberry	1/8

SING: O, Hetu!
Again: O, Hetu!

Which in the circumstances appears to be a very appropriate word to chant.*

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*Bryan, Cyril: The Papyrus Ebers, D. Appleton and Company, New York, 1931, p. 44-49.

Minimal Hypertension and Insurance Mortality

A Plea for Early Treatment

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THERE ARE indications which point to the desirability of treating the early minimal hypertensive patient in order to prevent avoidable excess mortality. In a study of 3,900,000 entrants[1] contributed by twenty-six life insurance companies from 1935 to 1953, the increased mortality of minimal hypertension is clearly demonstrated. It is well to bear in mind that these blood-pressure recordings were made during the normal working day and that these subjects represent a large group of people who can be considered to be apparently normal, healthy individuals living normal lives.

Age vs. Mortality

Most physicians would not treat as a hypertensive a 35-year-old man with a blood pressure of 144/90; yet the expected mortality over a ten-year period of 1,000 standard risks at this age would be 20. In the Build and Blood Pressure Study of 1959,[1] it was revealed that males in this group with no other impairment had a mortality ratio of actual to expected deaths of 199%. With this mortality of 199%, 40 men would die during this same ten-year period.

Forty-five-year-old males with a blood pressure of 156/95 were found to have a mortality ratio of 336% — an excess mortality of 108 lives out of a thousand in a ten-year period. The increased death rate is due principally to cerebrovascular accidents and diseases of the heart including coronary heart disease.

The Borderline Hypertensive

Objections are made to the possible variables that can occur during the life insurance examination. The Medical Letter[2] states that the examining doctor under-reads the blood pressure often enough so that "it would be a serious error not to consider the possibility that this practice is sufficiently widespread to have a marked effect on the outcome of the study." On the other hand, a frequently heard objection is raised by William Evans[3]: "A slightly raised blood pressure met with in applicants for life-assurance benefits . . . is inseparable from the natural anxiety and excitement peculiar to this special examination." Therefore, it is of more than passing interest to note the incidence of arteriosclerotic heart disease experience in a four-year follow-up of the Framingham Study[4] of borderline hypertensive patients without heart disease. The rate was found to be 62 per thousand as compared with 26 per thousand in normotensives. Borderline hypertension was defined as that between 140/90 and 160/95. If men with high relative weight and high cholesterol were omitted, the rate for subjects with borderline hypertension

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*Associate Medical Director, Northwestern National Life Insurance.

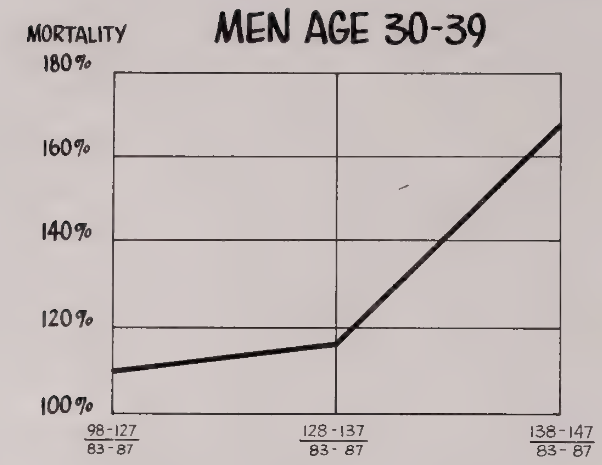

Figure 1

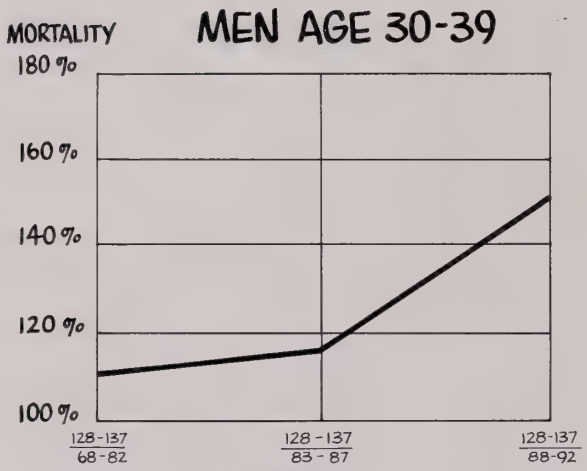

Figure 2

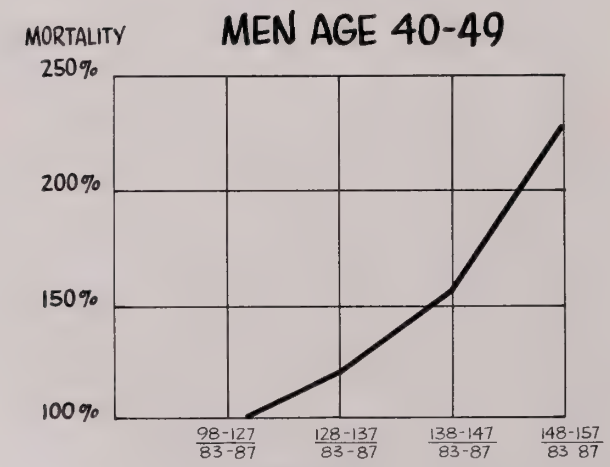

Figure 3

would be 37/1000 as compared with 17/1000 for normotensive persons.

Treatment of the Hypertensive

As important as it is to treat severe hypertension, it is even more important to treat the early minimal hypertensive patient in an effort to stave off the increased mortality that can be statistically demonstrated in minimal hypertension. Several studies[5-9] reveal frequent reversibility of cardiac failure, cardiomegaly, abnormal electrocardiograms, and retinopathy, with only moderate success in the treatment of severe hypertension. Moyer, Heiden, Pevey and Ford[5] stated that although there was no difference in renal function in treated patients in the group with mild to moderate blood-pressure elevation between the control period and the follow-up period of twenty-eight months, the similar, untreated group showed a reduction in renal blood flow from 966 cc./minute to 755 cc./minute. In the group with severe hypertension there was no change in renal function before and following treatment; however, the comparable untreated group showed a marked reduction in function in only twenty-four months. Significant improvement in electrocardiograms and decrease in heart size were noted in both treated groups. Van Dyne[6] reported improvement in renal function, retinopathy, heart size, and electrocardiographic changes in twenty treated cases. Newman and Robertson,[10] in a report on 22 cases, feel that there is little doubt that adequate control of the blood pressure is a major factor in preventing the recurrence of cardiac failure in patients with hypertension. Kirkendall and Armstrong[11] were able to demonstrate a "very active repair process" in the form of widespread collateral circulation to effectively bypass the obstructed arterioles of the retina in treated hypertensives. If these changes can be reversed, it should be reasonable to assume that they can also be prevented.

Reversibility of Hypertension

Hypertension hastens the process of arteriosclerosis. The rate of change is undoubtedly dependent upon many factors, such as the severity and the duration of hypertension and the individual response to it. It has been contended, however, that keeping the blood pressure normal or reduced will not prevent hypertensive complications.[12] Housel, Kelly, and Daly,[13] on the other hand, state that earlier treatment of hypertension by the family physician is virtually preventing hypertensive encephalopathy and malignant hypertension from being seen, whereas twenty years ago several cases could be observed on the wards of any large hospital on any day. Smirk[14] feels that grade four retinal hypertensive changes rarely occur in a patient whose blood pressure is properly treated. Studies demonstrate not only the reversibility of abnormalities but also a definite decrease in mortality with effective treatment and control. Moyer et al.[5] reported a mortality of 25% in a treated group with an average survival time of 22 months. Their untreated group had a mortality of 75% with an average survival period of 11 months. Their study of 31 patients with malignant hypertension revealed only two of 13 treated patients dead, with an average survival time of 30 months as contrasted to the untreated group in whom the mortality was 17 out of 18 patients, with an average survival period of 14 months.

Treatment vs. No Treatment

Leishman,[15] in a study of 400 cases, reported far fewer deaths among patients whose hypertension was treated either by surgery or with drugs, the mortality rate being roughly one third of that observed in the untreated cases. The incidence of cerebral hemorrhage was markedly reduced.

Aurell and Hood,[16] in an analysis of postmortem and case records, found that the mortality from cerebrovascular lesions was decreased in patients with controlled hypertension and that no patient was under continuous good regulation of blood pressure at the time of the stroke.

In a study of 2,775 patients treated medically or surgically before and after 1950, Kinsey, Sise, and Whitelaw[17] showed a statistically significant decrease in the five-year mortality rates in the medically treated cases.

In a 10-year follow-up, White[18] reported the effectiveness of surgical treatment as compared with no treatment. Perry and Schroeder,[19] in a four-year study, showed a significant lower mortality rate among the 209 medically treated cases.

The Cause of Death in Hypertension

The effects of hypertension were graphically illustrated by Clawson[20] in a review of 2,597 fatal cases. Death was ascribed to myocardial insufficiency in 43%, to coronary artery disease in 36%, to cerebral hemorrhage in 14%, and to renal insufficiency in 7%. Obviously, it is almost impossible to demonstrate at what level of hypertension these changes begin to occur; however, there is strong indication that hypertension is already well established at levels of 140/90, with this figure being statistically more significant in the younger age groups. Mortality increases slightly from the lower levels of blood pressure up to 140/90; but at this point the curve rises sharply (Figures 1 and 2).

Labile hypertension is also often considered unimportant. In a study of 2,510 policyholders who were considered substandard risks solely because of mild elevated blood pressure, Pollack, McGurl, and Plucinski[21] found that the differences in mortality between the nonlabile group and the labile group were not statistically significant.

The Systolic vs. Diastolic Pressure

There is a common belief that if the

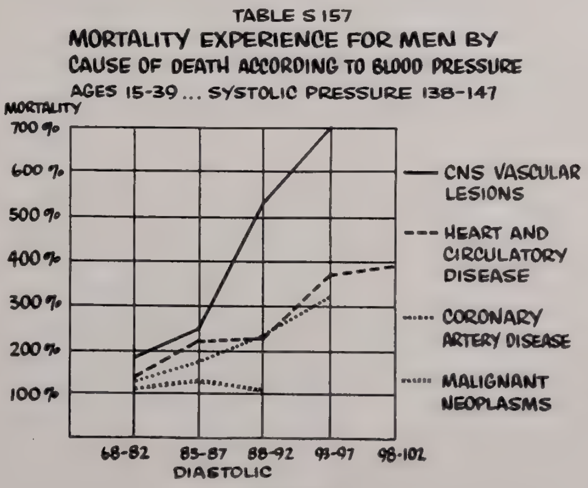

Figure 4

systolic pressure rises, it is not harmful as long as the diastolic level remains normal. That this is incorrect is well illustrated in Figure 3 which clearly depicts the rapidly rising mortality with increasing systolic pressures in the presence of a normal diastolic pressure.

Much is said about a "basal" blood pressure which is obtained after a period of recumbency. If this reading is normal, then the patient is not classified as hypertensive. How valid is this criterion? Does it reflect the true physiological process? Is it the condition that prevails during problem and stress situations, e. g., in driving and in other daily competitive situations? Are we in a position to say that it is of no consequence if the blood pressure is increased during the waking hours as long as it is normal while at rest or sleep? Life insurance statistics based on blood pressure readings obtained during the working day indicate that this is not so. In males under 40 with blood pressure in the range of 138/88 to 147/92, fatal heart disease is more than twice and cerebral vascular accidents more than five times as frequent (Figure 4).

Conclusions

Any objection raised in regard to the manner and means of blood pressures obtained from life insurance examinations cannot explain the orderly, constant, and definite increase in mortality seen with every small increment of increased blood pressure starting with levels that are considered low.

Reassurance in the treatment of early hypertension was acceptable when there was little else to offer; but this does nothing to increase the hypertensive patient's longevity. With the safe, effective antihypertensive drugs available today, the physician can no longer ignore slight elevations of blood pressure any more than he can ignore the early signs of any other disease process. The significantly increased mortality in early hypertension clearly defines the physician's responsibility.

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11-21 May be secured from the author or the reprints.

STARLING'S LAW*

If the inflow, and consequently the outflow, of blood from the heart is kept stable, the work that the heart has to do is greatly altered by a change in the peripheral resistance. As a result of incomplete emptying the residual blood can increase the diastolic volume, with consequent rise in the venous pressure. Due to an associated lower arterial pressure, there would be a poorer coronary blood supply, and the heart would become fatigued, and bradycardia could result.

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*See Minnesota Med page 594.

Total Right Hepatolobectomy

for A Metastatic Neuroblastoma

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For most of a decade partial hepatectomy has been performed for benign and malignant primary tumors and cystic lesions of the liver. In the past few years metastic tumors in the liver have also been excised when the site of origin was believed to be under control. Woodington and Waugh in 1963 reported a 20% 5-year survival in 25 such cases, with an operative mortality of 4%. In their series, as in most, the majority of the metastatic tumors have involved the left lobe of the liver.[19]

Wangensteen[17] reported the first total right hepatectomy to be successfully performed in this country in 1951. In 1953 Pack and Baker[14] outlined the technique of controlled resection of the right lobe of the liver — a technique now generally accepted.

The majority of hepatic tumors in children are fortunately benign and many are best left undisturbed.

Of eighteen hepatic tumors in children cited by Gross,[6] all of which were surgically explored, only five were resectable; two of the eighteen children survived: one a child with a hamartoma locally excised and the other an infant with multiple hemangiomas which were later treated with radiation therapy.

Mersheimer in 1953[12] and Clatworthy in 1956[3] reported the first successful right hepatolobectomy case reports for malignant tumors in children. Gross attempted right hepatolobectomy for metastatic neuroblastoma but lost the child due to an air embolus.[7] Clatworthy has since been interested in this subject but does not have a case where right hepatolobectomy has been carried out in a child for metastatic disease.[4]

Removal of up to 80% of the liver substance has been successful in experimental animals. Pack and Islami[15] cite regeneration in rats within 12 to 18 days and in dogs within five weeks following resection of large portions of liver. They further discuss a patient reoperated two years after total right hepatic lobectomy, where regeneration produced final liver dimensions greater than the original liver size. They suggest that regeneration might be influenced by cortisone administration and, further, that the inevitable elevation of portal pressure in the remaining left lobe is highly beneficial in promoting rapid regeneration.

Case Report

A four-year-old white male was first admitted to St. Vincent's Hospital on January 19, 1964, because of a large slightly tender mass in the right upper quadrant. He was otherwise asymptomatic. A chest roentgenogram and pelvis films were normal. Intravenous pyelography revealed a normal but displaced right calyceal system; intravenous cholangiography revealed delayed filling and displacement of the gallbladder to the left. A complete blood count, urinalysis, bilirubin, prothrombin time and cephalin flocculation were within normal limits. VMA determination[18] was .76 micrograms per 24 hours.

Initial Procedure

On January 23, exploration of the abdomen through a right rectus retracting incision revealed a metastatic nodular involvement of the entire right lobe of the liver. The left lobe appeared normal. The nodular enlargement of the right lobe was continuous with a huge mass originating in the region of the right adrenal gland. The kidney was entirely separate from this mass and displaced downward. The mass was considered unresectable at that time. A biopsy of a representative portion of the liver edge revealed undifferentiated neuroblastoma.

The patient received a tumor dose of 1025 roentgens over a period of two weeks and was then discharged from the hospital on February 8, 1964. After considerable re-evaluation it was the consensus of opinion that the child should be re-explored with the prospect of resecting the tumor-containing right lobe of the liver.

Definitive Procedure

At the time of readmission on March 9, 1964, the liver mass was approximately 50 per cent smaller than prior to radiation. On March 10, two right inferior vena cavagrams were carried out at the suggestion of Dr. William Clatworthy, Children's Hospital in Columbus, Ohio. Since there was no encroachment or roughening of the vena cava, right hepatic lobectomy under general anesthesia with moderate hypothermia was done on the following day. At this time the patient weighed 16 kilograms (35.25 lbs.).

Findings

At operation the large multinodular mass was found to involve only the right lobe of the liver, with a border of 2 to 3 cm. of normal appearing tissue just to the right of the falciform ligament. The left lobe of the liver was free of any irregularity. One periportal lymph node, examined by frozen section, contained only inflammatory tissue. There were no other periaortic nodes, nor was there any evidence of spread into other areas of the abdomen.

Technique of Operation

The cystic duct and artery were identified and separately ligated and divided. Following this the right hepatic duct and right hepatic artery were isolated, doubly ligated and divided. At this point the liver was lifted slightly and the adrenal gland dissected from its bed. The right adrenal vein was then isolated, and five or six smaller hepatic veins draining into the vena cava were also isolated, ligated and divided without difficulty. The bare area of the liver was next separated from the diaphragm with extreme care as the vena cava was approached. The portal vein was then visualized, making it apparent that there was actual tumor growing into its bifurcation; therefore, the portal vein was transected at a point 2 cm. proximal to its bifurcation, where it was widely patent. An end-to-end anastomosis of the left lobe branch of the portal vein to the main portal vein was made out, using #00000 arterial silk, thus allowing an adequate inflow of the portal vein blood into the remaining left lobe of the liver. The anterior surface of the liver just to the right of the falciform ligament was then incised, giving greater mobility to the specimen and to the remaining two large hepatic veins that were still attached to the vena cava near the diaphragm.

Operative Complications

At the junction of one of the large hepatic veins with the vena cava a laceration developed and an air bubble was noted moving slowly along the inside wall of the translucent vena cava. Constant positive pressure-bag breathing by the anesthesiologist allowed quick recovery of the air bubble, and the rent in the cava was repaired with #00000 arterial silk suture. It was in a difficult location, however, and a considerable amount of time elapsed from the onset of the positive-pressure breathing.

Bradycardia

Just as the laceration was closed, the patient developed a marked bradycardia and an idioventricular rhythm. The pericardium was quickly opened and the heart was found to be quiet, flaccid and empty. Cardiac massage and 1 cc. of 1:1000 adrenalin into the right ventrical reinstituted a normal rhythm.

Completion of Operation

The remainder of the operative dissection was straight forward, the liver transection passing through the left edge of the quadrate and caudate lobes. The common duct was not drained. Gelfoam was applied to the cut edge of the liver as there was insufficient falciform ligament to reperitonealize this raw surface. The wound was then closed in conventional fashion. Two large Penrose drains were led out from the bare area on the under surface of the diaphragm. Two chest tubes, one from the pericardium and one from the right thorax, were led out of the ninth thoracic interspace and attached to Glover suction.

Estimated blood loss was approximately 1850 c.c.; the patient received 1700 c.c. of whole blood during the procedure. On the following day his hematocrit was 40% and hemoglobin 13.8 gm.

The Specimen

The specimen removed weighed 760 gm. and measured 16 x 14 x 8 cm. As noted at operation the intrahepatic portal vein contained gross tumor, but the cut edges along the left border and the posterior surface of the specimen were not involved.

Postoperative Course

Cardiovascular

The patient's EKG pattern was nodal following the cardiac arrest, but towards the end of the operation it reverted to a normal sinus rhythm with good P-waves. As the patient was rewarmed during the first few hours postoperatively, his EEG pattern reverted to normal. Constant venous pressure monitoring for the first three postoperative days was accomplished by an inferior venacava catheter which had been left in place following the cavagram performed the day before. His venous pressure determinations were used as a means of titrating small volume salt-free albumin and blood administration needs at one to two-day intervals. His urine output was measured hourly, and his postoperative hemoglobin determination stayed in the range of 12.5 to 13.5 gm. with an appropriate red blood cell count.

Blood Chemistries

The morning of surgery the patient's chemistries revealed the following in milliequivalents: sodium 138, potassium 5.1, chloride 99, with a total protein of 7.9 gm. per cent. His prothrombin time was 39% although he had not been on anticoagulants. On the second postoperative day his alkali reserve was 24, potassium 4.1, sodium 126; and his chlorides were 78 milliequivalents. These last two were promptly corrected to chlorides and sodium of 94 and 138 milliequivalents respectively by the following day. Two days after operation following a good postoperative day and as the patient was gradually being warmed, he developed a transient seizure. His fasting blood sugar was 40 mg. per cent. He improved markedly with the intravenous administration of 25 c.c. of 50% glucose. On the following morning he became lethargic and quite unresponsive. His fasting blood sugar then was 20 mg. per cent. Immediately after the intravenous administration there was a quick clearing of his lethargy, and he sat up in bed and talked.

Nutritional Intake

For the next several days until his blood sugar levels became stable, he received, in addition to his regular fluid and electrolyte requirements, occasional intravenous injections of 25 c.c. of 50% glucose. By the fourth postoperative day the abdominal wall drainage from his Penrose drain sites had lessened considerably. He was given 12.5 gm. of salt-free albumin on that day and the next. By the fifth postoperative day he was ambulated and his urine output was quite constant at about 700 c.c. each 24 hours. His oral intake of up to 1000 c.c. of fluids allowed reduction of intravenous fluids.

Convalescence

On the sixth postoperative day his temperature rose to 102.4 rectally. His electrolytes were then normal. His Penrose drains had been removed the previous day. He also developed a peculiar tremor of his hands and arms reminiscent of the "liver flap" seen in cirrhotic adults. By the eighth postoperative day he seemed stronger but remained irritable; his tremor became less prominent, coincident with an increased oral protein intake. At this point he developed a pericardial friction rub.

Antibiotic Medication

His temperature continued to spike daily to 102 to 104 degrees, and on the tenth postoperative day he was placed on Achromycin. The following afternoon he developed marked abdominal distention and hyperperistalsis and had a number of loose green bowel movements. The Achromycin was then discontinued. Chloromycetin was started on the thirteenth postoperative day, but the temperature spikes continued. Although the patient seemed otherwise improved, his abdomen remained slightly distended and diffusely tender; but there was no localized area to suggest an abcess. Films showed slight elevation but good motion of the diaphragm. At about this time he was transfused with 250 c.c. whole blood on two separate days. The chloromycetin was discontinued and Unipen* (Sodium Nafcillin) was started on the seventeenth postoperative day with a prompt improvement in his temperature curve toward normal. The child continued to do well and improve in appetite and activity. His abdomen remained moderately distended during this period of time. His friction rub disappeared.

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*Wyeth Laboratories.

By the thirteenth postoperative day ascites was noted, which gradually subsided without paracentesis. His abdominal girth decreased, antibiotics were stopped, and his early sedimentation rate of 80 mm. dropped to 16 mm. in one hour. His electrolytes and complete blood count were normal, and his prothrombin time was 68% at the time of discharge on April 5, 1964, twenty-five days following right hepatolobectomy. He was subsequently seen in the office and continued to make a satisfactory recovery with further reduction in girth of the abdomen, increase in weight and improvement in strength and color.

Subsequent Fate

Between August 1964 and January 1965 he was placed on chemotherapy using Vincristine sulphate. Pulmonary metastases were noted which regressed for three months, then grew rapidly, leading to death in February 1965.

Discussion

Neuroblastoma, to be cured, must be diagnosed early and treated radically. Those children with visceral metastases generally have a much better prognosis than those with skeletal involvement. Gross[8] reports that 98% of children with bony metastases die. Surgery, irradiation and chemotherapy are the modalities employed jointly for the treatment of neuroblastomata in most children's medical centers. Swenson,[16] however, believes that neuroblastoma should be simply biopsied and then treated by radiation if extension into the renal fossa makes removal hazardous. Chapman and Sheridan[1] found that radiation did not materially increase the 30% 14-month survival figure in their series of 32 patients. The Boston study indicates that 99% of the deaths occur within two years after diagnosis.

Gross and associates[8] advocate radical surgical removal of all available gross tumor, followed by postoperative radiation up to a total dose of 3600 to 4000 r. Complete removal of tumor followed by irradiation in 21 such patients resulted in an 88% two-year survival. Even where palliative excision of the great bulk of the tumor and x-ray were used, 64% of 14 patients survived for two or more years, even though in these instances it had been obvious to the surgeon that some tumor had remained.

The operative technique was greatly facilitated by the adequate exposure provided by the thoracico-abdominal incision and incision of the diaphragm radially towards the vena cava.

Ligation and division of the cystic duct and cystic artery are no problem, but careful isolation of both the right and left main branches of the portal vein is essential.

The separation of the diaphragm from the bare area of the liver affords a clear approach to the junction of the large hepatic veins with the vena cava and, in addition, increases mobility of the specimen. Ligation and division of adrenal veins and six to eight smaller, short hepatic veins that pass from the right lobe into the vena cava must be done with extreme care to avoid hemorrhage and air embolus.

Air embolus is a real entity and can lead to death if unrecognized. If the anesthesiologist quickly increases the positive pressure on his breathing bag, venous return to the right heart is restricted. This is helpful in that the air bubble will drift distally and emerge from the cava at the site of the tear or leak.

Transection of the liver 1 to 2 cm. to the right of the falciform ligament is facilitated by a dusky line of demarkation, evident through Glisson's capsule, representing the effect of ligation of the right hepatic artery.

The bradycardia, idioventricular rhythm* and subsequent cardiac arrest occurred because we failed to heed Starling's Law.**

Protracted breathing allowed recovery of the air bubble and distention of the vena cava facilitating its repair; but, as a result, cardiac and coronary filling were incomplete. Had we punctuated this period of bag breathing even occasionally to allow the lung parenchyma to fill properly, perhaps we could have avoided the cardiac arrest.

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*See Test Your Word Score Page 607.

**See page 590.

The abnormal prothrombin time suggesting a depletion of glycogen stores was not adequately protected with 5% and 10% glucose intravenously to avoid the profound hypoglycemia we observed.

Conclusions

After biopsy and radiation therapy, regression in the size of the tumor can occur sufficiently to provide an otherwise inoperable lesion of the liver.

Removal of up to 80% of the liver substance has been successful in experimental animals. Pack and Islami[15] cite regeneration in rats within 12 to 18 days and in dogs within eight weeks following resection of large portions of liver. They further discuss a patient reoperated two years after total right hepatic lobectomy, where regeneration produced final liver dimensions greater than the original liver size. They suggest that regeneration might be influenced by cortisone administration and further suggest that the inevitable elevation of portal pressure in the remaining left lobe is highly beneficial in promoting rapid regeneration.

A case of successful right hepatic lobectomy for metastatic neuroblastoma is presented.

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12-19 May be secured from the author or the reprints.

BERENDES SYNDROME*

Fatal Granulomatous Disease of Childhood

This syndrome was first described by Berendes, Bridges and Good in 1957 and is characterized by recurrent suppurative lymphadenitis, chronic dermatitis, chronic pulmonary disease and hepatosplenomegaly. The disease is usually familial, occurring in males with the onset of bacterial infections in the first year of life. The course is usually progressive with continuous or recurring infections. Death occurs between four to 13 years of age, usually of extensive lung involvement but has also resulted from hepatic disease or from septicemia. Pathologically there is granulomatous formation present in the lungs and liver with an unusual abundance of plasma cells. No bacterial, fungal or mycobacterial agents have been recovered from these lesions. To date the underlying physiologic defect leading to repeated bacterial infections is unknown. Adrenal steroids when used with antibiotic therapy appear to have a suppressive effect on the progressive course of this disease.

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*See Minnesota Med 40:309, 1957 and page 580, this issue.

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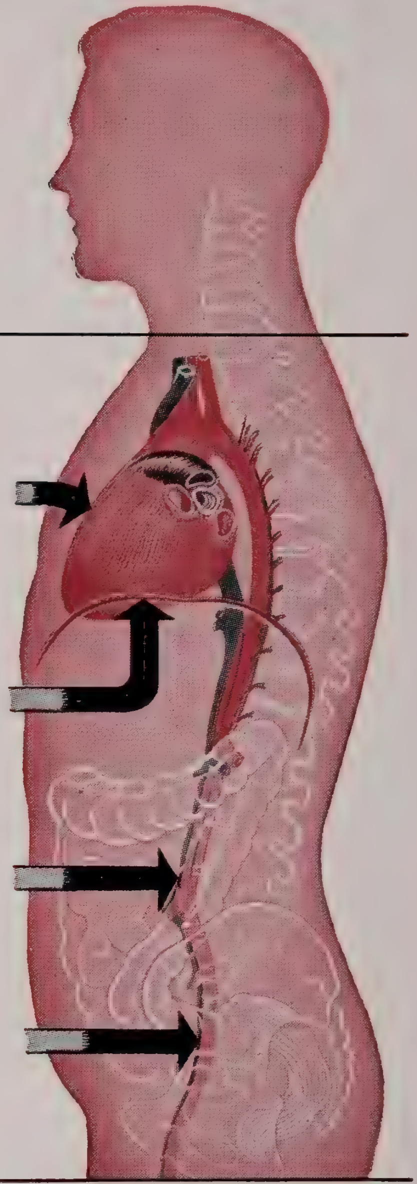

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Editorials

The Management of Bell's Palsy

BELL'S PALSY can produce a serious and permanent disability. Unfortunately, for years it has been assumed that 80% of patients recover spontaneously. Dr. Jerome Hilger,* in the November issue, has pointed out that, in fact, only 55% of patients have a complete return of function.

In our modern society, which demands much personal contact, great importance is placed on one's physical appearance; thus the psychological, as well as financial, disability of one who must meet the public with a deformed, twisted face can be appreciated.

Although a permanent partial or complete facial paralysis does not threaten the patient's life, the treatment may be compared to that of a patient who has acute appendicitis. In acute appendicitis only a small percentage of patients die of their disease, but because the treatment is so successful and the possible effect of the disease so serious, most, if not all, are subjected to appendectomy.

In recent years the results of surgical decompression have vastly improved, and the side effects of the treatment have been reduced to only the temporary time loss and discomfort of operation. With modern otologic microsurgical techniques, the patient can be expected routinely to experience no further damage to the facial nerve by the surgery, to have no postoperative hearing loss or loss of balance, and, probably most important to the patient, to have no postoperative cavity. Except for the insignificant scar from the incision, the patient's physical appearance is in every way the same as it was before operation.

Initially, a careful neuro-otologic examination is necessary to make the diagnosis of Bell's palsy by exclusion of other lesions. The exact level of involvement can be determined by testing the various branches of the facial nerve. It is useful for the surgeon to know whether the greater superficial petrosal nerve is functioning, as determined by ability of the involved side to produce tears; whether the stapedius nerve is functioning, as detected by determining the presence or absence of the stapedial reflex to loud sound; or whether the chorda tympani nerve is functioning, as tested by either chemicals or an electric taste tester.

A patient with complete Bell's palsy can be treated medically, and the treatment often is effective in producing a cure. The basic problem is to determine which patient should have surgical decompression and when such decompression should be carried out. In this respect, it is important to follow some general guidelines, especially in situations which carry a poor prognosis: (1) Facial-nerve decompression is indicated in all patients who have Bell's palsy accompanied with pain. (2) Decompression is indicated if there is no sign of recovery within three weeks of the onset, regardless of test results. (3) Surgical

Continued

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*See Minnesota Med 48:1463, 1965.

Anatomy of
Low Back Pain #1
the sedentary life
is often the seat of
low back pain

The human spine is not engineered fo prolonged sitting at desks, pianos, typewriters and drafting boards. The stresses set up by the heavy, forward-tilted head and trunk, balanced precariously on an insufficient base, result in strain of the dorsal musculature, particularly at the low lumbar level.

The unusual muscle-relaxant and analgesic properties of 'Soma' make it especially useful in the treatment of low back sprains and strains. 'Soma' is widely prescribed ☐ **to relieve pain** ☐ **to relax muscles** ☐ **to restore mobility.**

Indications: 'Soma' is useful for management o muscle spasm, pain, and stiffness in a variety o inflammatory, traumatic, and degenerative musculoskeletal conditions. It also may act to normalize motor activity in certain neurologic disturbances.

Contraindications: Allergic or idiosyncratic reactions to carisoprodol.

Precautions: 'Soma', like other central nervous system depressants, should be used with caution in patients with known propensity for taking excessive quantities of drugs and in patients with known sensitivity to compounds of similar chemical structure, e.g., meprobamate.

Side Effects: The only side effect reported with any frequency is sleepiness, usually on higher than recommended doses. An occasional patient may not tolerate carisoprodol because of an individua reaction, such as a sensation of weakness. Other rarely observed reactions have included dizziness, ataxia, tremor, agitation, irritability, headache, increase in eosinophil count, flushing of face, and gastrointestinal symptoms.

One instance each of pancytopenia and leukopenia, occurring when carisoprodol was administered with other drugs, has been reported, as has an instance of fixed drug eruption with carisoprodo and subsequent cross reaction to meprobamate. Rare allergic reactions, usually mild, have included one case each of anaphylactoid reaction with mild shock and angioneurotic edema with respiratory difficulty, both reversed with appropriate therapy. In cases of allergic or hypersensitivity reactions carisoprodol should be discontinued and appropriate therapy initiated. Suicidal attempts may produce coma and/or mild shock and respiratory depression.

Dosage: Usual adult dose is one 350 mg. tablet three times daily and at bedtime.

Supplied: Two Strengths: 350 mg. white tablets and 250 mg. orange, two-piece capsules.

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intervention is also indicated when nerve excitability is absent or is decreasing with the daily tests. (4) Decompression should be considered for the patient whose appearance has an unusual importance for his livelihood.

Finally, physicians should be aware of the poor spontaneous recovery rate of complete facial paralysis as a result of herpes oticus. Almost all patients with such infection have serious permanent disability. In these patients, the nerve involvement is usually in the petrous portion of the temporal bone. Likewise, basilar skull fracture may involve the petrous portion of the temporal bone. Since the entire facial nerve is surgically accessible, decompression in either of these two uncommon conditions should not be delayed.

Jack L. Pulec, M.D.
Rochester, Minnesota

Patch-Grafting of the Gastrointestinal Tract

CLOSURE OF A large defect in a hollow viscus can be a formidable task. Large perforations resulting from ulceration of the duodenum or distal part of the esophagus are common examples of this problem. Other causes are trauma and resection of invasive malignant lesions. When primary closure cannot be made by suturing the margins of the defect together, other techniques must be used.

In the January issue of MINNESOTA MEDICINE, Thal and associates[1] describe patch-grafting of defects in the gastrointestinal tract with the seromuscular surface of an adjacent loop of bowel. They also used this method of grafting for large defects in the urinary tract. When considering this method of closure for defects in the gastrointestinal tract, one must take note of the authors' warning about grafting in the duodenum and stomach. They have shown experimentally that seromuscular patch-grafting is not applicable to the stomach or first part of the duodenum unless measures are taken to ablate acid production. Otherwise the incidence of perforation of the graft is extremely high.

Full-thickness pedicle graft of intestine offers another method for bridging a large defect in the duodenum. A segment of jejunum, excised from continuity but with mesentery and blood supply intact, can be opened longitudinally on the antimesenteric border and sutured to the margins of the defect. This type of graft might be less susceptible to immediate perforation than a seromuscular graft, but the incidence of subsequent perforation would undoubtedly be high unless measures were taken to reduce gastric acid production.

Donald C. McIlrath, M.D.
Rochester, Minnesota

Reference

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Relevance of the Spread of Cancer Cells to Chemotherapy

AS EARLY as 1869 tumor cells were demonstrated in the circulating blood. Since then many studies have further established the presence of cancer cells in the peripheral circulation, in blood vessels draining tumor sites, in the bone marrow, in lymphatic tissue, and in various body cavities. Even though the greater percentage of tumor cells released into the blood stream from a large primary tumor fail to survive, this spread of such cells may be responsible for the death of a cancer patient as the invading cells interfere with normal cell functions. The success of excisional surgery for malignancy is limited, therefore, because of the frequency with

Continued

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which cancer cells are transported to distant sites.

Prevention of cellular spread is difficult, as it most likely takes place continuously once the tumor has invaded blood vessels and lymphatics and penetrated into a serous cavity. Many methods have been accepted by surgeons in attempts to prevent this spread, such as (1) early ligation and division of the veins draining the tumor sites, (2) occlusion of the bowel lumen on each side of the tumor, (3) covering of the tumor-bearing tissue, and (4) limited manipulation of the tumor. Certain drugs, such as nitrogen mustard, when used to wash a wound at the time of surgery, have been found useful for destroying cells. Many drugs given internally have also been found to be ineffective against solid tumors either because these drugs are too toxic for the host to endure or because their anticancer properties are limited.

No positive method of increasing host resistance to malignancy in humans has been demonstrated, despite the many successful experiments in the field of chemical carcinogenesis.

The finding of tumor cells in the blood should not be used as evidence that radical surgery for malignancy is unjustified, as we know that the tumor-cell-destroying capacity of the host is evidenced by the disappearance of large numbers of cells from the blood. Though it is also true that the identification of tumor cells in the peripheral blood of a patient with a malignant disease is associated with a significantly decreased survival, this identification of such cells does not indicate a fatal outcome for all patients. The course of the disease may be changed by curative surgery, by decreased infectivity of the disseminated cells, by chemotherapy, or by host resistance factors. Further work in the field of adjuvant chemotherapy and host resistance is vital for an increase in survival rates of cancer patients.

George E. Moore, M.D., Ph.D.*
Sigmond H. Nadler, M.D.*
Buffalo, New York

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*Department of Surgery, Roswell Park Memorial Institute, New York State Department of Health.

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4. Moore, G. E., and Sandberg, A. A.: The Occurrence of Malignant Cells in the Peripheral and Regional Circulations. E Acta Un Int Cancr SVI: 405, 1960.

Aneurysmal Abscess

ALTHOUGH NOT common, infection can involve the walls of arteries to the point of dilatation and aneurysm formation. The aorta, pulmonary arteries, or the peripheral arteries may be involved. Invasion can result from (1) embolization of organisms, (2) entrance of organisms at site of previous disease or degeneration, and (3) direct extension from an adjacent suppurative process. The classic example of the first type is the mycotic aneurysm secondary to subacute bacterial endocarditis. With regard to the second type, there is sufficient precedence to suggest that diseased arteries are susceptible to bacterial invasion, for example, damaged heart valves and patent ductus arteriosus. In recent years the term "cryptogenic" has been applied to a type of mycotic aneurysm caused by deposition of bacterial organisms at the site of atherosclerosis.[1] In these aneurysms, as contrasted with endocarditis cases, results of blood cultures often are negative (the causative organisms are *Salmonella* and *Staphylococcus*) and the effects of intensive antibiotic therapy are disappointing. The ef-

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fective treatment of mycotic aneurysm is surgical, with excision of the diseased tissue and graft substitution.

Early symptoms may be nonspecific, with only malaise and fever, but eventually a tender, pulsating mass presents itself. The tendency of mycotic aneurysms to rupture eventually has been stressed by several authors.

True mycotic aneurysm must be differentiated from false aneurysm, which results from complete rupture of all coats of an artery, in which the lumen then communicates with a sac whose wall consists of periarterial structures and clot; and which also results from secondary hemorrhage due to septic erosion of a contiguous artery. Secondary hemorrhage may present as a rapidly enlarging pulsatile mass. Into this latter classification, the infected pulsating hematoma, the cases of Drs. Huebl and Read* more properly belong. As pointed out by the authors in the January issue, the treatment of the dual problems of infection and vessel destruction is difficult, and prevention of the initiating causes must be the first order of defense.

Francis J. Kazmier, M.D.
Rochester, Minnesota

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*Huebl, H. C., and Read, R. C.: Aneurysmal Abscess. 49:11, 1966.

Reference

1. Blum, Lester, and Keefer, E. B. C.: Clinical Entity of Cryptogenic Mycotic Aneurysm: Report of Six Cases. JAMA 188:505, 1964.

Pulmonary Surgery for Emphysema

It is well known that cysts can occupy most of one side of the thorax without causing apparent disability if the opposite lung is normal. It is imperative to assess patients with air cysts critically by a complete battery of pulmonary function and blood gas-tension studies. It is likewise imperative to understand the operative indications and hazards. There are four types of cysts.

A Single Bulla in an Otherwise Normal Lung

The pulmonary function is normal, and operation could be advised to prevent chronic recurring infections and to prevent compression of normal lung parenchyma.

Multiple Bullae

There usually is well-preserved ventilatory function. Diffusing capacity may be normal or reduced, depending on the status of the remaining lung. A vigorous medical approach should be advised to prevent further destruction of remaining lung tissue.

Bullae as Part of Generalized Emphysema

There is severe ventilatory impairment, a low diffusing capacity and, frequently, abnormal blood gas tensions. Operation usually is contraindicated and is extremely hazardous; a vigorous medical program is indicated.

Cysts and Bullae Related to Cystic Degeneration of the Lung

This is seen in the honeycomb lung in histiocytosis X, scleroderma, and chronic diffuse interstitial fibrosis. Operation is of no benefit because the pathologic process is diffuse.

I think that the term "emphysema" implies chronic irreversible obstructive airway disease and that bullae are part of the generalized pulmonary disease. The best chances for good results depend on early recognition and a vigorous approach to medical treatment.

David E. Dines, M.D.
Rochester, Minnesota

Reference

1. Hymes, A. C., and Berkas, Ernest M.: Pulmonary Surgery for Emphysema. Minnesota Med 49:50, 1966.

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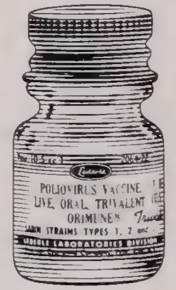

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In infants vaccination should not be commenced before the sixth week of life. Do not give to patients with viral disease, or if there is persistent diarrhea or vomiting. ORIMUNE and live virus measles vaccine should be given separately.
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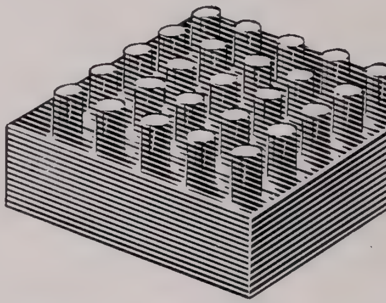

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*Rosenthal, S. R., Nikurs, L., Yordy, E., and Williams, W.: Scientific Exhibit Presented at the Annual Meeting of the National Tuberculosis Association, Chicago, Illinois, May 30-June 2, 1965.

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Intracerebral Hemorrhage

Of the many varieties of cerebrovascular disease, intracerebral hemorrhage continues to be, once it is fully developed, a frustrating and difficult disease to manage. The pathologist also finds that analysis of the evolution of the condition to its final picture is difficult because the underlying or associated pathologic changes are often distorted or destroyed by the end result of the pathologic change, the hemorrhage itself.

Epidemiologic studies indicate that the incidence of intracerebral hemorrhage has decreased during the last several decades. This lowered incidence is likely the result of potent antihypertensive treatment, which reduces the degree of hypertension itself as well as minimizes the secondary arteriolar changes. Chason[1] and his associates point out that clinical hypertension was invariably present in patients who died of intracranial hemorrhage. More than three fourths of their patients had, on pathologic examination, hypertensive changes in the vessel. It is hoped that continued use of antihypertensive medication will lead to a further reduction in the incidence of hypertensive intracerebral hemorrhage.

Many other diseases cause, though much less frequently than hypertension, intracerebral hemorrhage. Every physician should remember that small hemorrhages occur and remain within the substance of the brain and that such hemorrhages generally are not fatal. Because the spinal fluid usually is normal initially (slight zanthochromia may be seen in four or five days in some patients), a diagnosis of ischemic infarct may be made.

Robert G. Siekert, M.D.
Rochester, Minnesota

Reference

1. Chason, J. L., Mahoney, W. F., and Landers, J. W.: Massive Intracerebral Hemorrhage. Minnesota Med 49:27, 1966.

Test Your Word Score

Hypacusis — *impaired ability to perceive sound* (page 564).

Claudication — *limping — originally described in cases with occlusion of thoracic aorta* (page 566).

Zoonotic disease — *any disease in man acquired from one of the lower animals. Rabies is an example* (page 584).

Idioventricular rhythm — *associated with the cardiac ventricles alone* (page 594).

Kernicterus — *icterus occurring in infants with degenerative changes in the lenticular nucleus, subthalamus and Ammon's horn* (page 613).

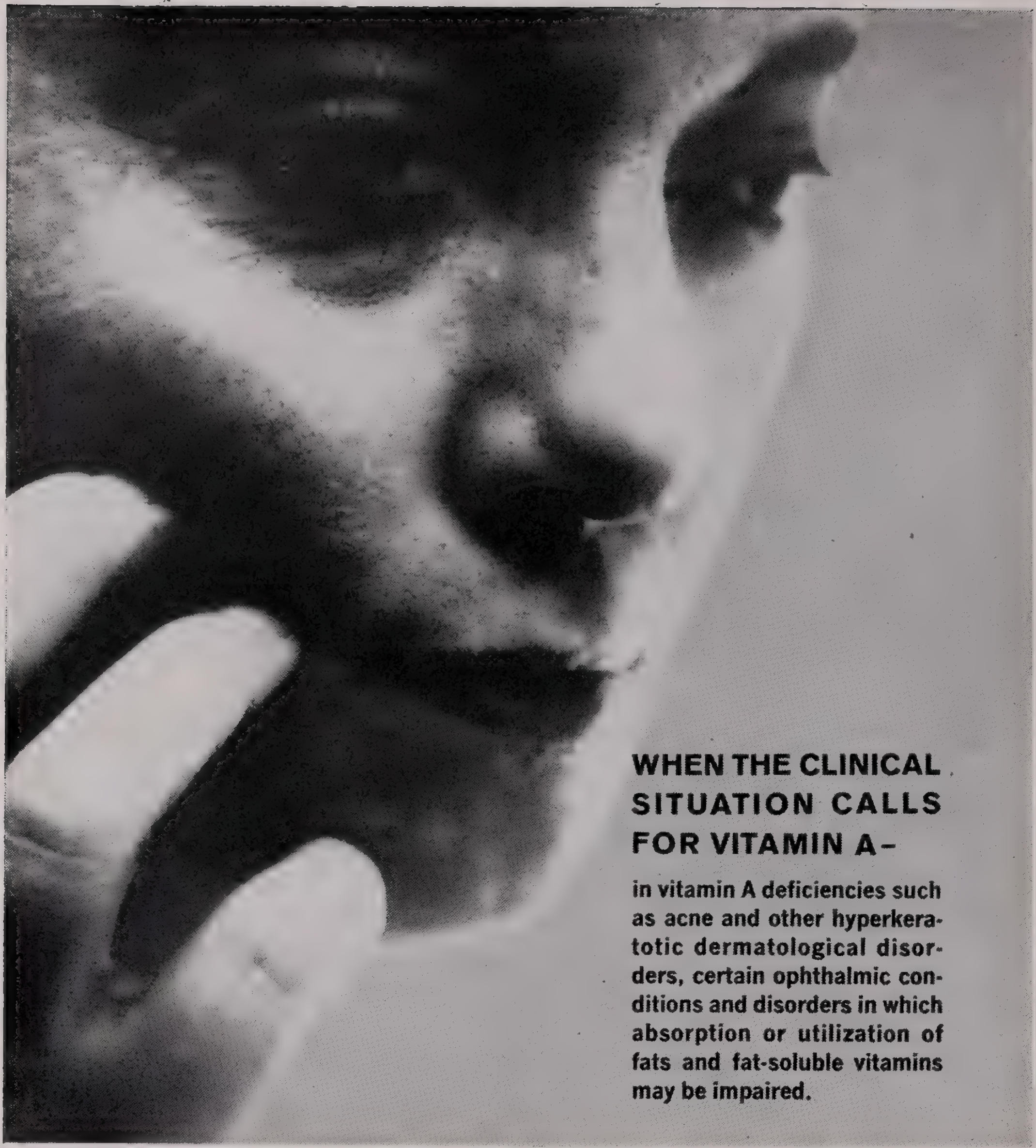
Anaplastic — *reverting to primitive cells* (page 623).

Apraxia — *a disorder of voluntary movements* (page 628).

Torulosis — *European blastomycosis* (page 643).

Paroxysmal — *recurring episodes* (page 664).

It is with narrow-souled people as with narrow-necked bottles; the less they have in them the more noise they make in pouring out. — Pope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Letter to the Editor:

Neither I nor any doctor is against essential vital statistics such as the central, hard-core information on the birth certificates. What I am complaining about is the peripheral information which now covers three sides of the birth certificate and which will certainly be extended to cover the fourth side unless a cure can be found: a cure for the disease of regimentation that is beginning to encompass all of us. The flood of paper work is just one of its symptoms. The five minutes it takes to complete these particular blanks are relatively insignificant except that they are the final straw on the back of the camel, the "one more case" that finally turns an endemic problem into an epidemic.

What possible use to anyone except a statistically inclined government worker are the questions pertaining to "date of mother's first marriage," or "years of education," or "illegitimate?" No one who delivers babies asks these questions as a part of the prenatal workup — why should they be necessary in the post-partum period? It is extremely unlikely that this information could add anything to the individual care of any patient; yet it is just this kind of information that is so dear to the statistically inclined people at all levels of state medicine. It is good that some doctors are interested in this phase of medical knowledge, but it should not be my job to do their leg work.

The chairmen of both the Maternal Mortality and the Perinatal Mortality Committees of the State Medical Association have told me that their committees have never made use of these supplements and that they have no plans to use them in the future. Yet the OB-GYN Committee for the State Association gave the official medical blessing to make the supplement possible.

Our time is valuable and in short supply. Let us conserve this precious commodity and parcel it out in areas where it will do the most good. Let us not add to our own burden by taking the time to fill in every blank that crosses our desks, for these blanks are a major manifestation of a serious disease that has already reached epidemic proportions. We can keep it from becoming pandemic only by drawing a line here and now. . . .

John E. Smith, M.D.
Minneapolis, Minnesota

The Editor's Soliloquy

The Fallacy of "I Read it in a Book"

People often quote the written word as if it were the gospel truth, defying the spoken word that denies it: "Put it down in black and white" or "I'll have to see it in print before I believe it." Even a self-evident spoken truth often seems to carry less conviction than the faintest ink. Why can't our word be as good as our bond?

"I saw it in the paper," "I read it in a magazine" appear to convey a finality that only a few cynical listeners would presume to challenge.

Our ingenuous belief in the incontestability of the printed phrase is

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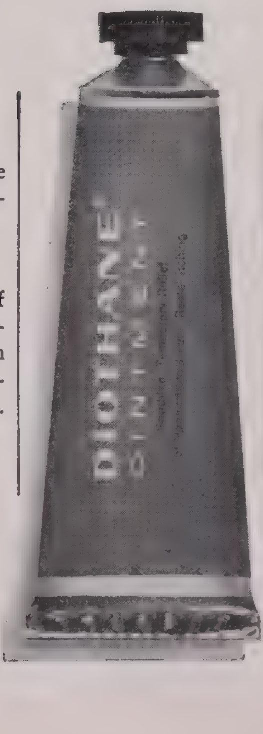

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apparently based on the fact that the iterated word is ephemeral and on repetition can be distorted; whereas the printed word, being concrete and permanent, is thereby invested with inviolability.

Perhaps historically and legally there are extenuations for our sublime faith in the printed word. Time was when literacy was confined to a very small minority of any population, and the illiterate masses, being in no position to prove otherwise, humbly assumed that all that these scholars read and wrote was the Truth, categorical and ex-cathedra.

Further credibility accrues to the printed word because a man can be held legally responsible for what he utters in print; for slander or falsehood he can be sued for libel. So we have deluded ourselves into assuming that greater care and calculation have gone into the selection of the printed word than into the impromptu choice of the spoken one.

But alas! we are still too naive! Our news and advertising media capitalize on our penchant for believing what we see in black and white. We easily succumb to slanted news propaganda and to blatant commercial advertising. As all that glitters is not gold, so, much that appears in print is far from being incontrovertibly true.

In this era of biased news and fulsome advertising, who would not credit the oral analysis of an impartial and objective news commentator more than the written lines of a prejudiced or chauvinistic reporter! And who would not give greater credence to the spoken word of a reliable doctor than to the printed blurb on a patent medicine advertisement?

But with the captivating charm of one who appeals to us, or the factual monotony of the other, like the drowsy drone of the greenfinch, how are we to know the difference?

Carl O. Rice, M.D.

Mom says: A perfectionist is a nice thing to have around the laboratory but a horrible thing to have around the house. — C.O.R.

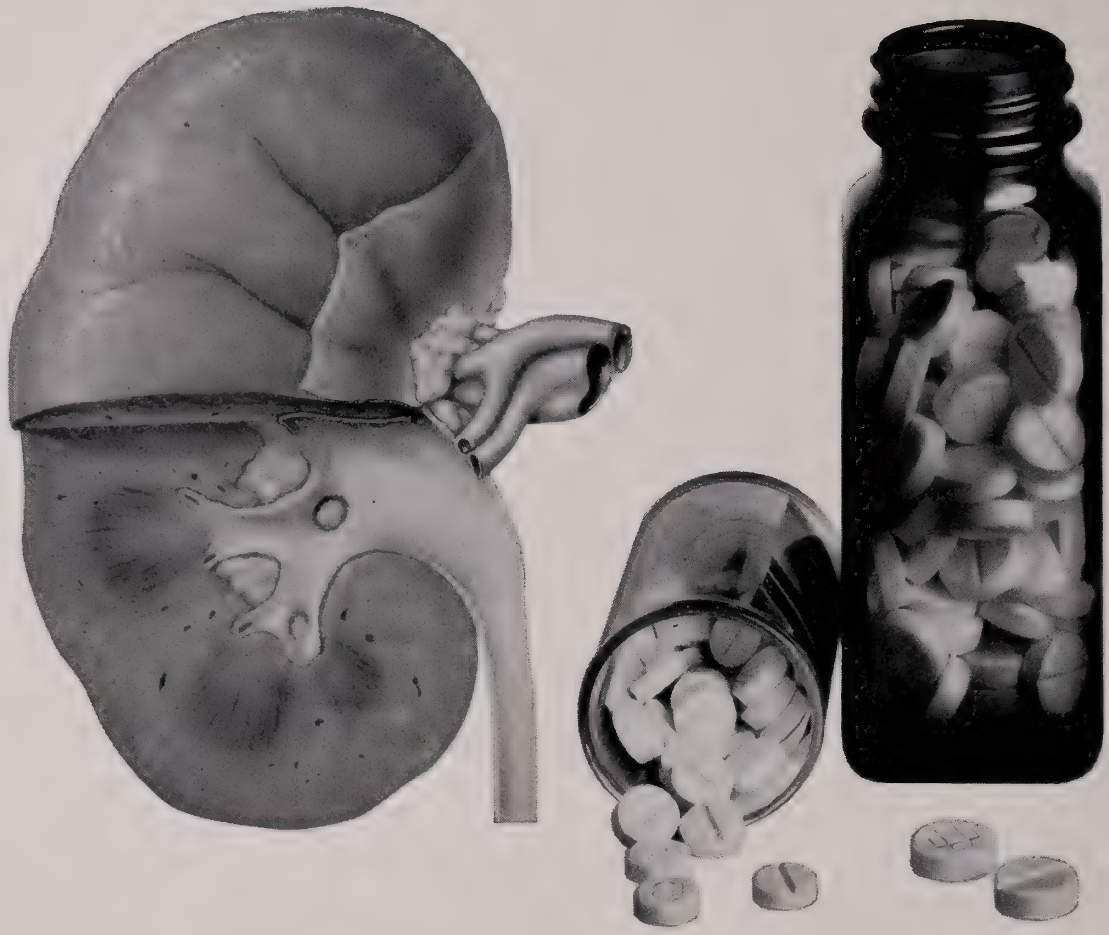
June 1966 Medical License Examination

At the February 11-12, 1966 meeting of this Board a request made by the President of the Senior Medical Class of the University of Minnesota Medical School was given consideration.

It was the determination of the Board that the request could be granted and the regular June, 1966 examination (which would regularly be held June 21, 22 and 23, 1966) was re-scheduled for June 14, 15 and 16, 1966 in order to accommodate graduates who wish to leave for their internships.

Minnesota State Board of Medical Examiners
J. P. Medelman, M.D.
Secretary

at Merck Sharp & Dohme...



understanding... precedes development

The development of chlorothiazide and probenecid were events of major importance, but perhaps even more important for the future was the Renal Research Program by which they were developed. When Merck Sharp & Dohme organized this program in 1943, it was expressing in action some of its basic beliefs about research:

- Many problems connected with renal structure and function were still undefined or unsolved. The Renal Research Program would begin its basic research in some of these problem areas.
- From knowledge thus acquired might come clues to the development of new therapeutic agents of significant value to the physician.

For example, the Renal Research Program put fifteen years into this search before chlorothiazide became available. But because these years had first led to a greater understanding of basic problems, the desired criteria for chlorothiazide existed before the drug was developed.

Along with other research teams at Merck Sharp & Dohme, the Renal Research Program continues to add new understanding of basic problems—understanding which will lead to important new therapeutic agents.

MSD **MERCK SHARP & DOHME** Division of Merck & Co., Inc., West Point, Pa.

where today's theory is tomorrow's therapy

Curbstone Consultation

Kernicterus*

QUESTION: How often does kernicterus occur in infants?

ANSWER: Kernicterus statistics vary depending on how the bilirubin is measured and how healthy the infants are in all respects other than jaundice. Kernicterus occurs in about 50% of infants with indirect bilirubin of 30 mg%. The disease has been reported at indirect bilirubin levels under 15 mg%, and infants have survived indirect bilirubin levels of over 35 mg% without kernicterus. Kernicterus is not easy to diagnose in its early stages.

The main features of the 1st phase are hypotonia, lethargy and poor suck; of the 2nd phase: spasticity, opisthotonus and fever; of the 3rd phase: diminution or disappearance of spasticity. The 4th phase appears in later infancy — extrapyramidal cerebral palsy.

An excellent article on the diagnosis of the different stages of kernicterus is Praagh's article in Pediatrics 28:870, December 1961. This author points out that 16% of the cases of kernicterus were unsuspected in the neonatal period.

Virginia Y. Blacklidge, M.D.
University of California
Berkeley, California

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*See Test Your Word Score Page 607.

Moderate Degree of Acne

QUESTION: Would you recommend the progestin-estrogen drug combination for a young lady who had severe acne in her teens but now has only a moderate degree of acne?

ANSWER: I would certainly recommend the progestin-estrogen combinations for a patient such as this, providing she has not responded to therapy as indicated above.

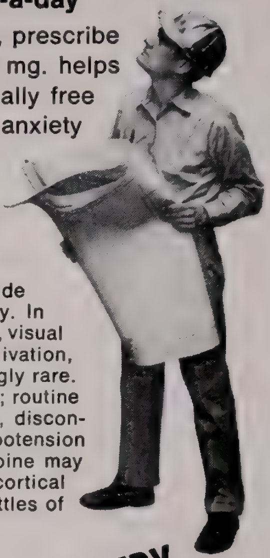
John S. Strauss, M.D.
Associate Professor
Boston University
Boston, Mass.

My diseases are an asthma and a dropsy and, what is less curable, seventy-five.
— Samuel Butler

We are all miscarriages, but some miscarry at three months after conception and some at 100 years after birth. — Samuel Butler

Blueprint for dealing with tension due to stress—Prolixin—once-a-day

For the patient who must be on the job mentally as well as physically, prescribe Prolixin. The prolonged tranquilizing action of as little as one or two mg. helps him cope with tension all day long. Markedly low in toxicity and virtually free from usual sedative effects, Prolixin is effective in controlling both anxiety associated with somatic disorders and anxiety due to environmental or emotional stress. Patient acceptance is good—because Prolixin is low in cost, low in dosage and low in sedative activity. Prescribe Prolixin.



Side Effects, Precautions, Contraindications: As used for anxiety and tension, side effects are unlikely. Reversible extrapyramidal reactions may develop occasionally. In higher doses for psychotic disorders, patients may experience excessive drowsiness, visual blurring, dizziness, insomnia (rare), allergic skin reactions, nausea, anorexia, salivation, edema, perspiration, dry mouth, polyuria, hypotension. Jaundice has been exceedingly rare. Photosensitivity has not been reported. Blood dyscrasias occur with phenothiazines; routine blood counts are recommended. If symptoms of upper respiratory infection occur, discontinue the drug and institute appropriate treatment. Do not use epinephrine for hypotension which may appear in patients on large doses undergoing surgery. Effects of atropine may be potentiated. Do not use with high doses of hypnotics or in patients with subcortical brain damage. Use cautiously in convulsive disorders. **Available:** 1 mg. tablets. Bottles of 50 and 500. For full information, see Product Brief.

WHEN TRANQUILIZATION WITHOUT SEDATION IS DESIRABLE, TRY

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THE SQUIBB TRANQUILIZER

SQUIBB FLUPHENAZINE HYDROCHLORIDE

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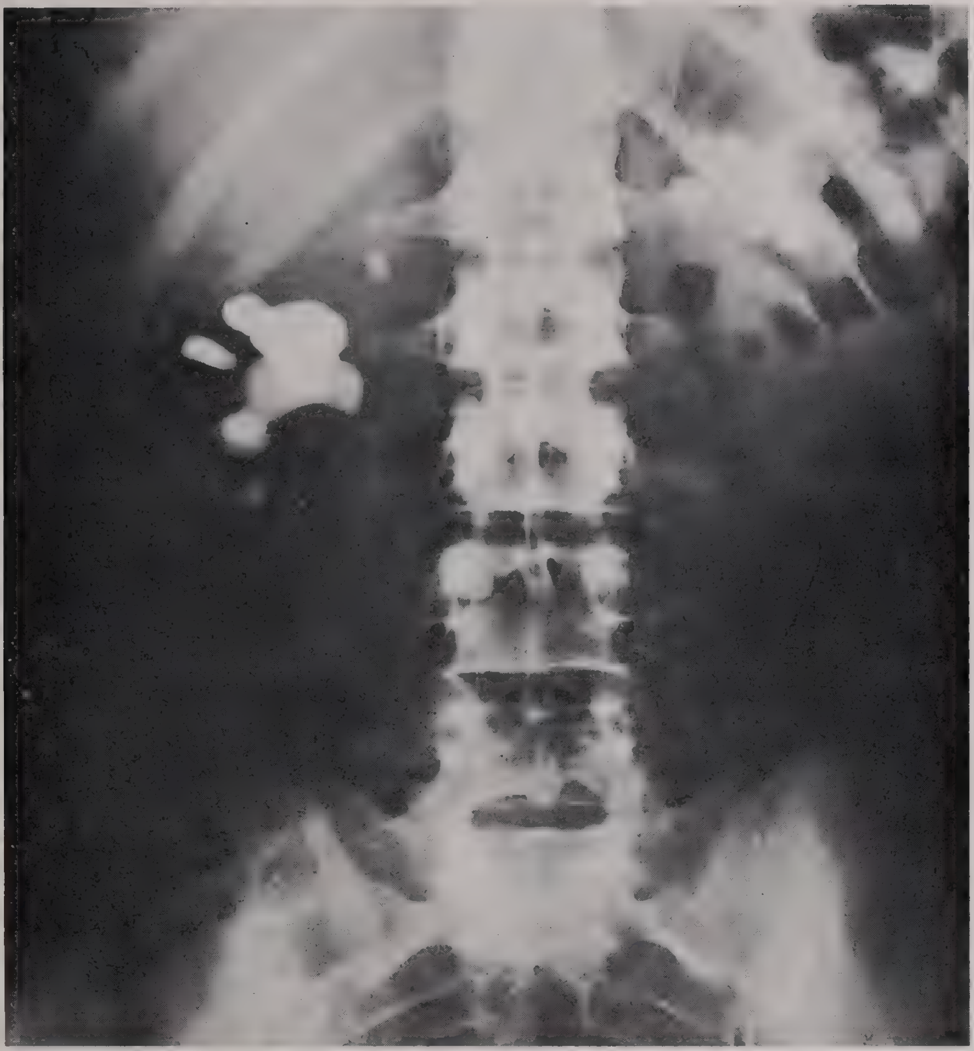
The Viewing Box



This 22-year-old white female was hospitalized because of weakness, nausea and vomiting. The past history revealed recurrent episodes of hematuria and renal colic secondary to urinary calculi since age 15. Three of nine siblings had urinary tract disease, one of whom developed urinary calculi.

Roentgen examination of the abdomen (Figure 1) demonstrated bilateral stag horn calculi plus numerous foci of renal parenchymal calcification in each kidney. The radiologist's differential diagnosis included:

1. Chronic glomerulonephritis or pyelonephritis.
2. Hyperparathyroidism.
3. Sarcoidosis.
4. Renal tubular acidosis.
5. Idiopathic hypercalcemia.
6. Hypervitaminosis D.
7. Primary hyperoxaluria.
8. Medullary sponge kidney.

What is your diagnosis? (See next page)

Diagnosis: Primary hyperoxaluria.

Primary hyperoxaluria is characterized by progressive bilateral calcium oxalate nephrolithiasis and nephrocalcinosis. A continuously high oxalate excretion is noted in the urine. The disorder usually begins in early childhood and leads to death from renal failure in childhood or early adult life.

Etiology is thought to be a metabolic defect leading to overproduction of oxalate. This condition has a familial incidence, but a definite hereditary pattern has not been established.

The roentgen picture consists of bilateral oxalate nephrolithiasis and nephrocalcinosis. Intravenous pyelography may be normal or demonstrate non-visualization secondary to calculus obstruction or renal failure. Radiolucent areas in long bone may signify deposition of calcium oxalate crystals.[3,4] The diagnosis of primary hyperoxaluria should be considered in all cases of nephrolithiasis and nephrocalcinosis noted in the first and second decades but particularly in a young child with a positive family history and without a demonstrable abnormality of calcium metabolism.

The patient presented had all the features of primary hyperoxaluria. A persistently high urinary oxalate excretion had been present since age 17. Onset at age 15 is somewhat unusual, as most reported cases note onset prior to five years of age.

Donald D. Dahlstrom, M.D.*
Minneapolis, Minnesota

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*Department of Radiology, V. A. Hospital and Hennepin County General Hospital.

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To the Student

To the student I would say, that however plain and simple may be our teaching, he must expect to forget much which he follows intelligently in the lecture-room. But it is not the same as if he had never learned it. A man must *get* a thing before he can *forget* it. There is a great world of ideas we cannot voluntarily recall, — they are outside the limits of the will. But they sway our conscious thought as the unseen planets influence the movements of those within the sphere of vision. — Oliver Wendell Holmes

To Remove a Bone from the Throat

As Jesus Christ drew Lazarus from the grave, and Jonah out of the whale, thus Blasius, the martyr and servant of God, commands, 'Bone come up or bone go down.' — Aetius (6th century A.D.)

The Tobacco Tyrant

Much smoking kills live men and cures dead swine. — George Prentice

. . . NOTHING, THAT IS,
EXCEPT THE SEDATIVE-ANTISPASMODIC
BENEFITS OF

DONNATAL®

There's nothing quite like a vacation to ease the pressures of the modern, "workingday" world. And for the patient who can't get away from it all, there's nothing quite like Donnatal to relax stress-induced smooth muscle spasm. For 31 years it has been the antispasmodic-sedative most often prescribed for relieving functional disturbances of tone and motility of the gastrointestinal tract.

belladonna alkaloids in optimally balanced ratio

In Donnatal, natural belladonna alkaloids are rationally balanced in a specific, fixed ratio that provides "the greatest efficacy with the smallest possible dose."[1] They avoid the clinical uncertainties of the variable tincture and extract of belladonna, and are considered superior in range of action to atropine alone.[2] Furthermore, they are generally recognized as being more effective than the synthetics for relieving visceral spasm.

phenobarbital for sedation

Years of clinical use have established phenobarbital as one of the most efficient and highly regarded sedatives. In fact, for general sedation it is the drug of choice.[3] In Donnatal, phenobarbital potentiates the spasmolytic effects of the belladonna alkaloids, lessening emotional tensions and checking the neurogenic impulses that trigger GI disorders.

more than 24 indications in PDR

Donnatal has withstood the test of time to become the classic sedative-antispasmodic because of its unsurpassed effectiveness, safety, economy, uniformity of composition, and dosage convenience. Its widespread acceptance and usage by the profession can also be attributed to its versatility in treating disorders characterized by smooth muscle spasm. There are more than two dozen distinct and separate indications for Donnatal listed in the current PDR.

IN EACH TABLET, CAPSULE, OR (5 cc.) OF ELIXIR

hyoscyamine sulfate	0.1037 mg.
atropine sulfate	0.0194 mg.
hyoscine hydrobromide ...	0.0065 mg.
phenobarbital	(1/4 gr.) 16.2 mg.

(warning: may be habit forming)

IN EACH EXTENTAB

hyoscyamine sulfate	0.3111 mg.
atropine sulfate	0.0582 mg.
hyoscine hydrobromide ...	0.0195 mg.
phenobarbital	(3/4 gr.) 48.6 mg.

(warning: may be habit forming)

BRIEF SUMMARY: Blurring of vision, dry mouth, difficult urination, and flushing or dryness of the skin may occur on higher dosage levels, rarely on usual dosage. Administer with caution to patients with incipient glaucoma, or urinary bladder neck obstruction. Contraindicated in acute glaucoma, advanced renal or hepatic disease, or a hypersensitivity to any of the ingredients.

REFERENCES: 1. Vollmer, H.: Arch. Neurol. and Psychiat., 43:1057, 1940. 2. Morrissey, J.H.: J. Urology, 57:635, 1947. 3. Krantz, J.C., Jr., and Carr, C.J.: Pharmacological Principles of Medical Practice, 2nd ed., Baltimore (1954), 552.

*This one at Westover, elegant Colonial Virginia plantation, located on the James River near Richmond. Built in the early 1730's by William Byrd II, founder of Richmond, it is now the home of Mrs. Bruce Crane Fisher.

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This precise Sanborn amplifier has convenient controls for recording the ECG, PCG, or ECG superimposed on the PCG . . . Cutoff Frequency . . . Audiophone Volume . . . and Sensitivity. Complete with contact microphone, cable and Audiophone (for use as an electronic stethoscope), Model 1506A is $450 f.o.b. Waltham, Mass. (continental U.S.). For more information, use the convenient coupon below. Sanborn Division, Hewlett-Packard Company, Waltham, Mass. 02154. In Europe, Hewlett-Packard S.A., 54 Route des Acacias, Geneva.

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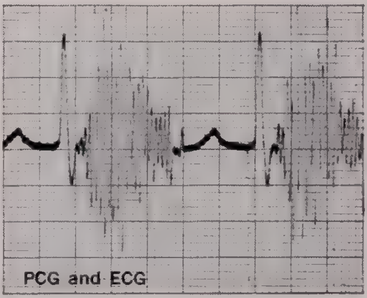
ECG



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Fracture–Trauma Conference

Orbital Floor Fractures

Swollen ecchymotic lids often mask the clinical picture of severe orbital injury. Since a black eye is so often associated with more severe head and body injuries, it may be neglected because it is "only a black eye."

The orbital rim consists of three bones: the frontal bone, the zygoma, and the maxilla. Immediately behind these heavy firm bones are some paper-thin, easily fractured bones. Fractures of these orbital bones may be clinically divided into two types: the external or rim fractures and the internal, blow-out fractures. A third not too uncommon group would combine the two.

Etiology of Orbital Floor Fracture

The orbital floor fracture was only recently explained in an interesting experiment by Converse and Regan[3] in which they placed a ball on the closed lids of a cadaver and struck the ball firmly with a hammer. On dissecting the orbit they found only a depressed comminuted fracture of the floor of the orbit. Next they exenterated a cadaver orbit, placed the ball on the orbital rim and struck it repeatedly with the same force as before. The floor of the orbit did not fracture—nor, for that matter, did the orbital rim. It is postulated then that the floor is fractured by the sudden increase in orbital pressure by the backward displacement of the globe. Interestingly, this backward "give" by the globe and the resultant floor fracture often protect the eye from serious damage such as rupture, choroidal tears, and intraocular hemorrhage.

Clinical Features

The clinical findings of a fracture of the floor of the orbit (besides the ecchymotic lids) may consist of any or all of the following:

Enophthalmos

The volumetric content of the orbit is increased by the depression of the floor, allowing the globe to rest deeper in the orbit — and sometimes lower in the socket. The vertical displacement may be more marked than the enophthalmos.

Continued

Ptosis May be Seen

This is not due to a levator palpebrae weakness but, because the globe is enophthalmic, the upper lid can hang down further on the eye (Figures 1 and 2).

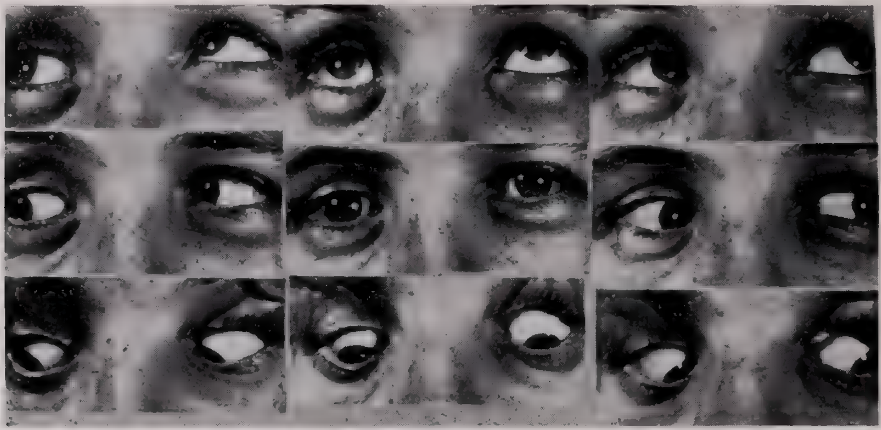

Fig. 1 — Pre-op fracture of floor of the orbit with incarceration of orbital contents. Note depression and pseudo ptosis of the left eye (most easily seen in straight-ahead gaze). There is also marked limitation of up gaze in the left eye.

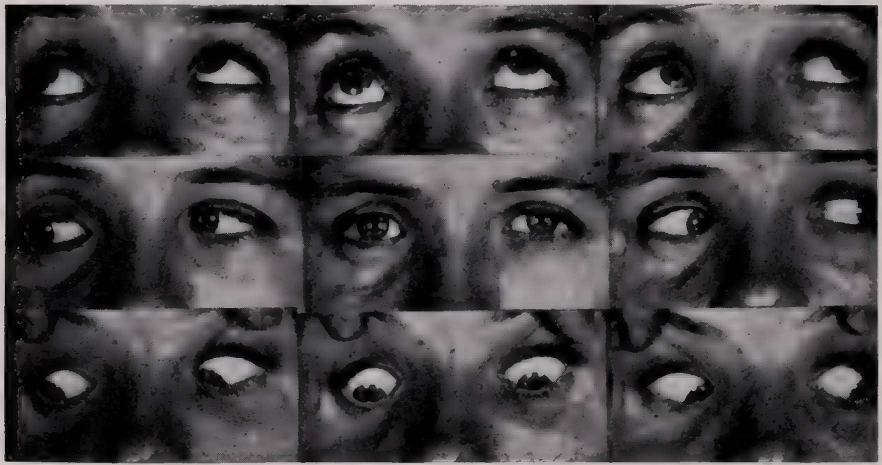

Fig. 2 — Post-op view — The floor of the orbit has been restored, with a normal cosmetic appearance and full ocular motility.

Limitation of Ocular Movement and Diplopia

These are usually due to the incarceration of the orbital contents, especially the inferior rectus and the inferior oblique into the fracture. There is usually limitation in up-and-down gaze, with diplopia in the up-and-down fields and single vision in the straight-ahead gaze.

Hypesthesia or Anaesthesia of the Cheek

When this occurs, it is due to trauma to the infraorbital nerve which passes through the floor of the orbit.

Diagnosis

Diagnosis of this fracture is by the clinical and x-ray pictures. The usual anteroposterior and lateral views are virtually useless in establishing the diagnosis. A Waters view is essential. On taking this x-ray, the head is tilted backward so that the tip of the nose and chin touch the film carrier. This orients the floor of the orbit in a plane perpendicular to the film and makes a depression of the floor easier to see. This view also rotates the sphenoid ridge below the level of the orbital floor, giving a good unobstructed view of the entire rim and floor.

The Orbital Rim

Fracture of the orbital rim may occur in any segment but occurs most frequently in the lateral and inferior rims. This fracture is always caused by direct trauma, usually from a fist or elbow, sometimes from the toe of a shoe and, with increasing frequency, from auto accidents.

The Zygoma

The zygoma is a strong dense bone which rarely fractures. Rather it separates at its sutures with the adjoining bone and also cracks in the arch, resulting almost invariably in three fractures: (1) At the zygomatico-frontal suture, (2) At the zygomatico-maxillary suture, and (3) In the arch. The bone is usually displaced inferiorly and rotated.

The Clinical Findings in Orbital Fractures

Flattened Malar Eminence

This is very disfiguring if left unrepaired, causing a rather easily noticed facial asymmetry.

Palpable Fracture

If there is not too much hemorrhage in the lids the fractures at the suture lines are easily palpated. With even a little zygomatic displacement and rotation, a "step-off" can be felt at the zygomatic maxillary suture.

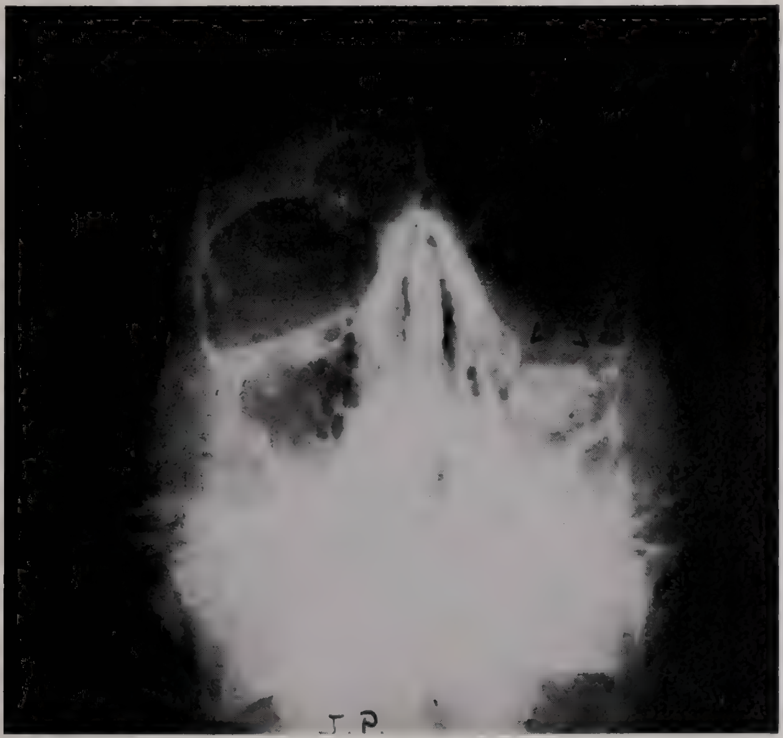

Fig. 3 — Waters view of an orbital rim fracture. Note the separations in the lateral and inferior rims. The underlying antcum is hazy because of hemorrhage.

Continued

Anaesthesia

Over the distribution of the infraorbital nerve anaesthesia may be found. This occurs because the fracture often extends through the infraorbital foramen, damaging the nerve.

Difficulty in Opening the Mouth Wide

This is due to the fracture of the zygomatic arch. There is sometimes an inward displacement of the arch, narrowing the temporal fossa, and impinging on the coronoid process of the mandible.

The diagnosis is easily made by the typical clinical picture and visualization of the fractures by x-ray (Figure 3).

Therapy

In the management of orbital injuries the following goals should be kept in mind: (1) Replacement of bony parts with restoration of facial symmetry; (2) Maintenance of ocular motility without diplopia; (3) Maintenance of jaw function and proper occlusion; (4) Treatment not delayed beyond two to three weeks when fibrocalcification of the wound begins.

The Orbital Floor

Treatment of an orbital floor fracture can be accomplished in several ways. It can be approached from below via a Caldwell-Luc type antrostomy. With this approach the floor of the orbit is digitally elevated and the position maintained by an antral pack or balloon. However, if an extraocular muscle is incarcerated between fragments, it will remain tightly fixed, and limitation of ocular rotation will persist. For this reason, I prefer a transorbital approach in which an incision is made in the lower lid at the level of the orbital rim. Periosteum is elevated off the floor, the fracture is located, and the incarceration freed. The floor can then be supported by overlaying it with autogenous bone, silicon or polyethylene plate, gelfilm plate or tantalum mesh or plate.

The Zygoma

Fractures and displacement of the zygoma can also be attacked in several ways. The bone can be elevated by the use of a transoral bar through the mouth beneath the zygomatic arch. It can also be elevated via an incision through deep temporal fascia from above the arch. Neither of these methods utilizes interosseous wiring. I prefer an open approach via the lateral rim over the fracture at the zygomatico-frontal suture. Holes are drilled above and below the fracture site, always entering posteriorly into the temporal fossa, rather than into the orbit. The zygoma is elevated by a malar hook or towel clip and the interosseous wire tightened. The zygoma usually stays in place without further wiring.

Conclusions

Simple black eyes may mask serious injury to the underlying bone. As the fractures may cause severe functional limitation, prompt therapy is urged.

Frederick C. Wuest, M.D.
Wayzata, Minnesota

References may be secured from the author.

Tumor Conference

Recurrent Thyroid Nodule Following Subtotal Thyroidectomy

The differentiation between Hurthle cell adenoma of the thyroid and Hurthle cell carcinoma often can be made only if it is known that there are no metastases. Hurthle cell carcinoma of the thyroid is not commonly seen. Although this particular type of thyroid is slow growing,[1] nonetheless, it grows both by direct extension and by metastasis and may eventuate in the death of the patient if unchecked by surgery or if preempted by death in some other manner.[2,3]

In many ways it is similar to papillary carcinoma of the thyroid. The mortality from papillary carcinoma of five years is quite low. Unfortunately, if followed long enough, a significant number of these patients can be shown to have died from their disease.[4] Even Crile, a strong advocate of suppressive hormone therapy, has pointed out that hormone-sensitive papillary carcinoma can over a period of time change into a highly malignant anaplastic* tumor and that all possible tumor in the cervical area that can be removed should be removed.[5]

The incidence of serious complications following a [straight-forward] thyroid lobectomy varies of course, but is, in fact, quite low if the surgery is performed meticulously in a bloodless field. This is the rationale that surgeons use to justify the removal of a rather large number of benign nodules. Let us ignore for the sake of this discussion the elimination of a sometimes symptomatic, worrisome lump to the patient. Surgeons and internists both get a somewhat skewed exposure to thyroid nodules, for both get a highly selected group of patients. The patient with a hard, painful, rapidly growing lump in the thyroid area often will go directly to a surgeon, whereas the patient with a soft barely palpable lump perhaps would consult his internist or general practitioner first. Nonetheless, if the criteria of malignancy are closely adhered to, as shown in large cancer centers, the diagnostitian can predict benignancy with an error as low as 2%.[6] When the incidence of morbidity and mortality of thyroidectomy, although admittedly low, is compared with this figure it does give some reason for being selective in operating upon thyroid nodules.

The incidence of serious complications following recurrent thyroid gland dissections is significant, and it is for this reason that recent emphasis has been on a complete lobectomy being done at the first sitting when

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*See Test Your Word Score Page 607.

Continued

the surgery is for a nodule. If such an operation has not been performed a recurrence of nodularity can occur, and the recurrence may be a different pathological entity, as the following case illustrates.

Case History

A 76-year-old female was admitted to the Hennepin County General Hospital for the evaluation of a mass in the right side of her neck. Thirty-five years previously she had had a subtotal thyroidectomy for hyperthyroidism. Twenty years prior to admission she had had a second thyroid operation to further control a recurrence of her hyperthyroid symptoms.

For the past twenty years she has been followed in the medical clinic. Ten days prior to admission a well defined mass in the region of the right lobe of the thyroid gland was discovered upon examination and she was admitted for evaluation. Her PBI was 8.6 mgm%; the BMR's were +17 and+23, and a I^{131} scan revealed no concentration in the area of the mass, but pickup was noted over the isthmus of the gland. No palpable cervical adenopathy was detected and a chest x-ray revealed no evidence of metastases. Surgical removal was recommended because the mass was well-defined, apparently rapidly growing, and nonfunctioning on the I^{131} scan.

Exploration of the neck revealed considerable scarring, and after some difficulty the recurrent laryngeal nerve was identified on the right side. No identifiable parathyroid tissue was discovered. A clean lobectomy was performed, removing the remaining isthmus as well. Frozen-section diagnosis was Hurthle cell carcinoma but with a capsule. Final diagnosis was Hurthle cell adenoma because no blood vessel involvement nor capsular invasion could be demonstrated. (Figures 1 and 2). The patient recovered well from her surgery with no voice problem and fortunately no evidence of parathyroid deficiency.

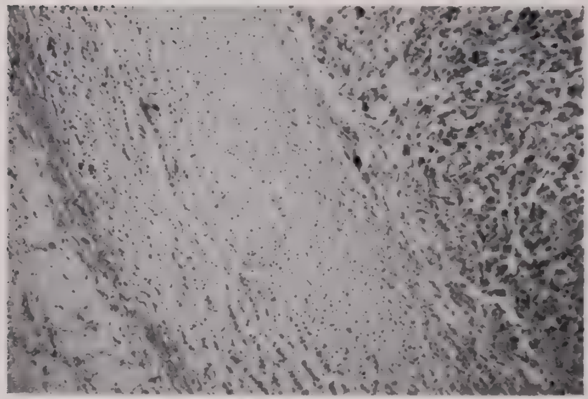

Figure 1

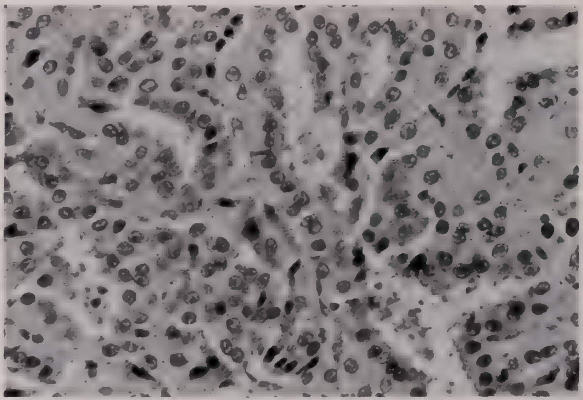

Figure 2

Discussion

This case demonstrates the point that the physician can not allow himself to be complacent in the evaluation of a thyroid nodule simply because he has prior evidence of a nonmalignant disease entity. He should evaluate a new nodule separately and with care. Whether or not he uses the I^{131} scan depends on personal preference. It would seem that its greatest use would be in proving functioning thyroid tissue in a nodule which the physician feels is benign from his own examination.

Nodules which are firm, fixed, or have shown rapid growth should be removed without delay. To this list should be added any nodule associated with cervical adenopathy or any nodule with associated hoarseness, dysphagia, or persistent cough.

Harrison H. Farley, M.D.
Minneapolis, Minnesota

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1. Chesky, V. E., Dresse, W. C., and Hellwig, C. A.: J Clin Endocr 11:1535, 1951.
2. Frazell, E. L., and Foote, F. W.: J Clin Endocr 9:1023, 1949.
3-6 May be secured from the author.

Neurological Conference

Management of Cerebrovascular Insufficiency*

Cerebrovascular disease is rapidly being recognized as a condition for which numerous therapeutic procedures and improved care are available. In extracranial insufficiencies involving the carotid circulation, an endarterectomy will often prevent an impending cerebral infarct. Anticoagulation also may provide a greater margin of safety against such a catastrophe when surgically inaccessible vessels are the cause of cerebrovascular insufficiency. Of equally great importance is the fact that a more optimistic attitude towards "stroke" patients who have developed a physical impairment such as hemiparesis or hemiplegia is appearing. To supplement physical therapy, speech therapy and vocational rehabilitation, education of the patient's family and friends concerning their relationships with the patient offers great potential for improving the happiness of a handicapped patient.

Doctor Louise Town*

A 52-year-old former real estate salesman was seen at the University Medical Center Clinics for the first time on July 7, 1965, complaining of the loss of use of his left arm, trouble with his speech, and dragging of his left leg. His present illness began in 1960 when he awoke one morning and found that he had difficulty talking and trouble writing with his right hand. Within a few hours his function had returned to normal. Subsequently, after consulting with his doctor, he was treated for high blood pressure. Repeated episodes of difficulty in talking occurred during the succeeding years. On these occasions, however, he developed weakness of the left side of his face, drooling from the left corner of his mouth and dragging of his left foot. The duration of each episode varied from one hour to as long as one day. During the past nine months he has had approximately 15 such attacks. Progressive motor weakness has developed in the left side of his body, including rather severe involvement of the left

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*Held on Thursday, August 12, 1965 at 4 p.m.

Sponsored by the U. S. Public Health Service Grant N2502A63. These conferences are an integral part of the Comprehensive Clinic Program at the University of Minnesota Hospitals. The pediatric conferences are held weekly from 1 to 2 p.m. every Wednesday. The adult conferences are held every Thursday at 4 p.m. Co-ordinators for the project are Dr. Edward C. Defoe and Dr. Charles Branthaver in Pediatrics and Dr. Robert Soll, in Adult Neurology.

*Student doctor, University of Minnesota Hospitals.

Continued

arm. His memory has gradually deteriorated and his ability to think has slowed considerably. At the present time he is depressed and cries easily. A weight loss of 20 pounds has occurred over the past nine months.

His significant past history includes two whiplash injuries in the last five years. Extensive hypertensive disease and numerous strokes have characterized his family history. There has been no history of diabetes or heart disease, however.

Physical Findings

During physical examination the patient had difficulty following directions and was generally noncommunicative. His blood pressure was 160/90 mmHg.; his pulse was 96 per minute and irregular; and his respirations were 12 per minute. Positive findings on general physical examination included arteriovenous nicking in the fundi, an increased pulsation of the right carotid artery compared to the left, and a soft bruit over the left carotid near the angle of the mandible. Neurological examination revealed a left central facial palsy and a left hemiparesis characterized by a rather marked spasticity and flexor contractions of the left upper extremity. There were positive Hoffman, Mayer and Babinski signs associated with hyperactive deep tendon reflexes on the left side, with functional strength significantly decreased in the left hand. The patient was able to walk, although paresis of the left lower extremity slowed his gait considerably.

Laboratory Evaluation

Laboratory evaluation was within normal limits with the exception of a three-hour post-prandial blood sugar which was 139 mg. per cent; however, a glucose tolerance test subsequently was found to be normal. Skull films revealed evidence of calcification within the carotid siphon and choroid plexus. Degenerative changes were present in the cervical spine, and calcium deposition was also noted within the carotids bilaterally on cervical spine films. The electroencephalogram revealed evidence of diffuse slowing predominantly over the right hemisphere. Our initial impression was that the patient had cerebrovascular insufficiency secondary to carotid occlusive disease.

The patient was admitted to the University Hospitals on July 31, 1965, for angiographic studies and consideration of vascular surgery. These studies were performed on the right and left carotid and vertebral arteries. Significant narrowing by arteriosclerotic plaques was found near the origin of both the right and left internal carotid arteries; in addition, an irregularity of the intradural portion of the left internal carotid artery and left anterior cerebral artery was noted. Considerable narrowing at the origin of the right vertebral artery was present.

Dr. Robert Soll*

According to the history the right hand was involved initially with speech in 1960, although subsequent episodes apparently have involved primarily his left side. Consequently, the history alone would make one suspect that bilateral disease was present. This would be a more likely explanation for his speech difficulty, since speech dominance is in the left cerebral hemisphere in 90% of cases, regardless of whether the patient is right or left-handed.

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*Neurologist, University of Minnesota Hospitals.

Intellectual Function

In a short interview preceding the examination, I realized that any test utilizing verbal interaction would probably produce little results; therefore, I approached him with the Peabody Picture Vocabulary Test, which consists of a series of pictures grouped according to progressively increasing difficulty in interpretation. With this test the examiner pronounces a word and the patient is asked to point to one of the pictures corresponding to the word. In this way we obtain an estimate of a person's intellectual functioning. On this particular test the patient received a raw score of 89 correct, placing his estimated IQ at about 78. Although we have no previous base line with which to compare these results, historically the patient's level of functioning would probably indicate that he has now suffered marked deterioration in his general capabilities.

Memory Defect

I then approached him with a few other tests in order to determine a possible memory deficit. On the Wechsler Memory Scale, which is a test to assess both recent and remote memory, he received a score of 61, whereas the average score is approximately 100; therefore, a significant memory deficit is also present. During this latter test I showed him a picture for 10 seconds and then asked him to draw what he saw. It was impossible for him to draw anything comparable to the designs. During this part of the test he suddenly said, "I can't see the drawing," although he apparently had been functioning very well before. It was at this point in the testing that the patient seemed to realize his deficit and manifested his frustration by retiring from the situation. A suggestion of this was brought out earlier in the interview when he abruptly stood up and said that he was going to get his wife, who apparently had been functioning as his spokesman since the onset of his speech difficulty. I called him back, telling him that we were interested in what he was able to do by himself, and he seemed to accept this. Nevertheless, he appears very sensitive about his deficiencies. Such an emotional reaction to realized loss of functioning has been noted among brain-damaged individuals and has come to be known as a "catastrophic" reaction.

Aphasia

In order to obtain an example of the aphasia that is present in this patient, I used a standard Binet Vocabulary Test, the only verbal test I used in this entire battery. I asked him to define the word "puddle," and he defined it as "a lot of this stuff that comes down out of the heavens makes a puddle." This is a classic aphasic response in that the patient has the concept in mind but is unable to give a precise synonym. To define the word muzzle, he said, "A bad dog." In the final test, the Porteus Mazes, he also did very poorly. The general conclusions from the entire battery of tests is that this man has suffered pronounced cerebral damage of a relatively diffuse nature, his problem of aphasia being his most severe difficulty.

Dr. Soll

It is possible that these tests may actually indicate a somewhat lower

Continued

result than is actually present. Some patients know what they are supposed to point at even though it may be simply a crude picture; however, they may be unable to do so because of an apraxia associated with a loss of speech and hearing.

Mr. James Gilbertson*

I might mention that the patient's performance on the Peabody Picture Vocabulary Test was good for the very easy items, whereas only when the pictures became more difficult did he have failures. In regard to the possibility of apraxia, however, I held the patient's jacket for him to put on when he was ready to leave and, when he had difficulty putting his good arm into the jacket, he turned about and attempted to put the jacket on backwards. This may be suggestive of apraxia.**

Miss Annie Laurie Baker†

At one time this man was very successful in business. He had been in the paint business for some time many years previously; but he eventually lost it. Then he went into new automobile sales and from that to selling second-hand cars. Failing in this venture, he lost almost all he had. Shortly after the onset of his illness he tried selling real estate but was unsuccessful. At that point, according to his wife, he lost confidence and became very depressed. He has remained so up to the present time.

There are two children in the family. The patient's wife is a high-strung individual, appearing frustrated by having to assume the responsibility for the family. This is of great concern to her, and she is hoping the children will eventually move back to be near their parents. For the last five years she has been the main financial support for the family, working as a secretary for the school nurse. Since this job employs her only ten months of the year, the family had a very hard time financially during the summer.

The daughter, a college graduate, is a social worker on the welfare board in another county; however, she is planning to leave this position and go to work for the welfare board in her home county in order to be with her parents. The son has had either two or three years of college. Apparently he has decided not to continue with his education. This is unfortunate, as he initially went to college on a scholarship. Since he is not returning to school, he has to repay this scholarship money which amounts to a considerable sum. The patient's wife remarked quite bitterly that, in order to keep the family going, she will probably have to sell the stock that an uncle left her. Social Security has been started for the patient, amounting to approximately $110 a month. The wife's income has been $200 a month, although she is now hoping to get a better job. Since they live in his mother's home, they fortunately do not have to pay rent. Although his mother is 83 years of age, she is very alert and is able to watch the patient during the day while his wife is working. I asked the wife what her husband did while she was at work, and she replied that he did nothing but sit on the davenport and watch television. As this is a family that is very confident and well known in their home town, I feel that once they become re-oriented they will be better able to carry on.

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*Clinical psychology trainee, University of Minnesota Hospitals.

**See Test Your Word Score Page 607.

†Director, Social Service, University of Minnesota Hospitals.

Dr. Soll

Mr. Gilbertson, knowing these facts about the patient could you speculate what level of intellectual functioning he had prior to his illness?

Mr. Gilbertson

I would think he would probably fall in the average to bright-normal range which is 100 to 110 IQ, but his present IQ shows that he is now markedly impaired. His present inability to read prevented us from giving him the Minnesota Multiphasic Inventory test. However, he seems to have suffered marked cerebral damage, resulting in deterioration in all areas of intellectual functioning.

Dr. Soll

In this type of patient the electroencephalogram usually manifests diffuse slowing in both cerebral hemispheres; however, in this particular patient the slowing was more apparent in the right hemisphere, which would be consistent with his physical findings which are predominantly left-sided, involving the left arm and leg.

Interpretation of Pulsations and Bruit

In this patient the pulsation of the right carotid artery compared to the left was strikingly greater. Such a finding is often erroneously interpreted, as the first impression is that the artery having the stronger pulsation also has the greater bloodflow. However, this is true only when the obstruction in the involved artery is more proximal to the heart than the point at which one is palpating the artery. On the other hand, if the obstruction or narrowing is distal to the point which is being palpated, the artery will actually pulsate more strongly, even though the flow of blood through that artery is less. The presence or absence of a bruit, either in the region of a carotid bifurcation or in the area of the origin of the common carotid artery at the base of the neck, is also extremely important. Such a finding presents strong evidence for suspecting a partial obstruction of the artery. Absence of a bruit on the other hand could indicate that the artery is either completely patent or totally obstructed. Since this patient had a left hemiparesis, a very strong right carotid pulsation, and no bruit in the right carotid artery, we felt that it was quite possible that his right carotid artery was completely obstructed near the level of the carotid bifurcation. The presence of a bruit in the left carotid artery near the angle of the mandible suggested that the blood supply through this artery was insufficient.

Surgical Correction

Surgical correction of an occluded artery by means of endarterectomy is virtually impossible, because clot formation distal to the point of obstruction has usually already occurred. Nevertheless, since this patient's mental and physical capacity had deteriorated considerably, we felt that the possibility of surgery should be evaluated by angiography in order to prevent further damage. As Dr. Town has already reported, angiography was performed on this patient, revealing partial obstruction of both the right and left internal carotid arteries. Since complete occlusion has not already occurred, the possibility of benefiting from an endartectomy still exists.

Continued

Dr. Shelley Chou*

The fact that the patient is having difficulty with his speech in the absence of the other right-sided findings is not unusual, since the speech area in the brain is quite sensitive to arterial insufficiency. If anything is done it would be for the purpose of preventing further deterioration of his neurological condition, particularly his dysphasia. In analyzing the angiograms, the more involved side certainly seems to be the right side. There are reasons for operating on either side. After hearing the discussions about his aphasia, perhaps the left side should be approached first.

Dr. Soll

How competent must the contralateral carotid circulation be to assure an adequate collateral cerebral circulation during the operation?

Dr. Chou

We don't have a cross-circulation study in this case. This could have been accomplished by injecting one side and concomitantly compressing the opposite carotid in order to determine how much of the circulation crosses the mid-line into the opposite hemisphere. Assuming there is no cross-circulation from the left to the right side, the risk of surgery in this case would be markedly increased. In order to reduce the risk, we would have to use a temporary shunt in the form of a silastic tube to bypass the segment of artery that was being operated on.

Dr. Richard Magraw**

What indications do you use for recommending surgical intervention in these patients with cerebrovascular insufficiency? Is finding a bruit on a routine examination an adequate indication, or must a patient have a history of a transient episode of insufficiency associated with a temporary neurological deficit?

Dr. Chou

We do not operate on the basis of physical signs alone but prefer to consider patients and their symptoms. We perform surgery to prevent deficits from occurring or from becoming permanent. If a permanent deficit is present we would infer that some damage to the brain tissue has already occurred. A patient who presents a complete hemiplegia of three or four days duration would be a poor candidate for surgery, since the likelihood of recovering function would be small even though the circulation might be re-established. The best candidate, would be one with minor and transient ischemic symptoms; however, we would not perform surgery on a patient who had had only one minor transient episode. The surgery is major in character, and there certainly has to be a very adequate reason for it. There is also some controversy about doing angiography on such a patient since it involves an element of risk. Assuming that angiography is performed and a large plaque visualized in an artery, I think surgery would be justified.

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*Associate professor, Neurosurgery, University of Minnesota Hospitals.

**Director, Comprehensive Clinic, University of Minnesota Hospitals.

Dr. Magraw

Is hemiparesis a fairly common occurrence in the course of doing an angiogram?

Dr. Chou

No, an angiogram generally is not risky, but there is a significant risk in the particular group of patients who have pre-existing disease in their circulatory system. Consequently, we are a little more careful with this type of patient. It is difficult to answer the question regarding how much improvement might be gained by surgery, because one operates on patients with various degrees of deficits. Some patients, curiously, have only mental symptoms or emotional lability. I would estimate roughly that 60% of patients will benefit by surgery. The mortality rate itself is not too high. We have had one patient who had a cerebral infarct prior to surgery and subsequently, following surgery, developed a hemorrhagic infarct and died.

Neurology student

How much reversal of this patient's mental deterioration might one expect if surgery was successful?

Dr. Chou

I think it depends on the type of mental deterioration present. If it is an episodic mental deterioration which could be explained on the basis of an ischemia one might expect a marked improvement. On the other hand, if a patient has shown progressive mental deterioration over a period of six months to a year, the likelihood for improvement is very small. It is interesting that 10% of our patients who have stroke symptoms have been found to have tumors.

Dr. Magraw

The Public Health texts state that the best measure of high quality health care being provided in an area is a preponderance of deaths from heart disease, cancer or stroke, with a minimal mortality from other causes. In years past many of us have been content to diagnose these so-called "strokes" and do nothing more. Now there is insistence that we do something more than simply diagnose and then write these people off as having had a stroke. A stroke is a "complication" of cerebral or extracranial vascular disease. In the next five or ten years we may become progressively more aggressive in attempting to prevent this complication.

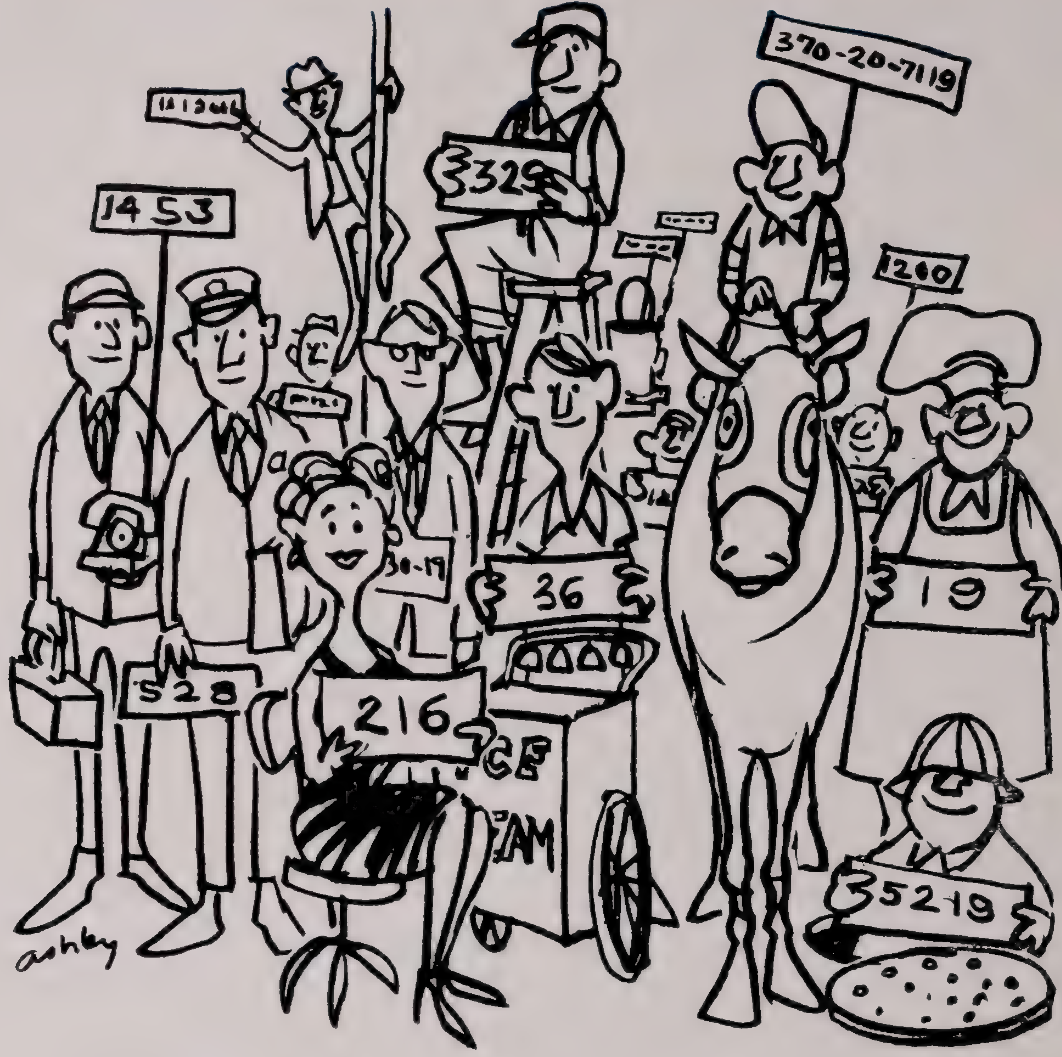
Addendum

It was elected to attempt carotid endarterectomy on this patient; however, during induction of anesthesia prior to surgery, the patient had a temporary cardiac arrest and the surgical procedure was cancelled. The risk accompanying any further attempt to do surgery was considered too great. Subsequent therapy has primarily involved helping the patient's family prepare to care for him after his return home.

Robert W. Soll, M.D.
Minneapolis, Minnesota

Participating in the conference were Dr. John Brantner, Assistant Professor, Clinical Psychology; Miss Annie Laurie Baker, Director, Social Service; Student Doctor Louise Town; Dr. Richard Magraw, Director, Comprehensive Clinic; Mr. James Gilbertson, Clinical Psychology Trainee; Dr. Shelley Chou, Associate Professor Neurosurgery, and Dr. Robert W. Soll, Neurologist.

BETTER SERVICE, DOCTOR? number 5 in a series



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Athletic Injuries

Maxillofacial Injuries in Athletics

Because maxillofacial injuries are a form of head trauma, one should first ascertain if there has been unconsciousness. Obviously, if the patient has sustained a significant cerebral concussion, he must be evaluated from that standpoint as well as for his possible maxillofacial injuries.

Probably the most common injury in contact sports is the contusion to the nose, causing epistaxis. Often this is associated with a fracture of the nose. Gross distortion makes diagnosis simple, but it is not always possible to determine a nasal fracture without x-rays. If bleeding is troublesome on the scene, a small amount of vaseline packing in each nostril will usually afford adequate hemostasis until the patient can be brought to the doctor's office or Emergency Room.

Facial lacerations obviously require immediate surgical care, including the sometimes forgotten tetanus toxoid booster. Important avulsed tissue, such as pieces of the nose or ear, should be saved because they can sometimes be replaced if they are in good condition.

Pain along the mandible should alert one to the possibility of a mandibular fracture. Inspection of the mouth should be done with adequate light. Often there will be a tear in the gingiva between the teeth in the presence of a mandibular fracture. If a fracture of the maxilla is suspected, one should also test the stability of the upper teeth to see if there is any movement. Probably the most important diagnostic aid is to check the occlusion of the teeth; most jaw fractures will cause malocclusion. This is usually evident both to the examiner as well as to the injured person. It might be well to add that loose teeth should not be pulled out at the scene of the injury. Many times they will tighten up spontaneously and it may be many months before anyone can be sure that a tooth is irrevocably devitalized.

Fractures of the malar or cheek bone produce ecchymoses and edema of the eyelids. If the floor of the orbit is involved, visual signs, such as diplopia, will usually occur. Contusions in this area may also cause paresis of the ocular muscles, also causing blurred vision or diplopia. Fractures of the malar often manifest themselves initially by flattening of the cheek or a palpably jagged fracture line along the infraorbital rim. Fractures of the zygomatic arch should be suspected if the individual has difficulty opening his mouth.

The diagnosis of significant maxillofacial injuries can often be made on the playing field, but more subtle injuries usually require not only x-ray studies, but more careful evaluation in the relative quiet of a doctor's office or emergency examining room. Because of the potentially serious problems, such as malocclusion, unacceptable cosmetic results, or visual aberrations as a result of these injuries, it is well to have appropriate consultation early.

Walter L. Lynn, M.D.
Minneapolis, Minnesota

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*See Minnesota Med 49:125, 1966 for fifth in this series. Sponsored by Minnesota Committee on Trauma of the American College of Surgeons.

"All Interns are Alike"

It stands to reason. They all go through the same training; they all have to pass the same tests; they all have to measure up to the same standards; they all are underpaid, too. Therefore, all interns are alike.

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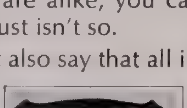
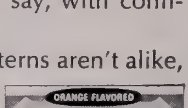
You might also say that all interns aren't alike, either.





Medical Seminar

Malignant Neoplasms of the Nasopharynx

Presented as a Seminar

Sponsored by

The Faculty of the Mayo Graduate School of Medicine

BECAUSE OF ITS insidious nature, cancer of the nasopharynx is commonly overlooked during its early stages and thus is one of the most lethal of neoplasms. This cancer constitutes from 0.3 to 0.4% of all forms of cancer and affects males three or four times more frequently than it does females. The cancer has been found in all age groups, from the very young to the very old, with a peak incidence in the fourth and fifth decades of life. The average age for males is 55 years while that for females is 49 years. The Chinese are said to be more commonly afflicted than are the other races.

Anatomic Considerations

Anatomically the nasopharynx extends from the base of the skull to the level of the free border of the soft palate. Its roof lies beneath the body of the sphenoid bone. The posterior wall is smooth and dotted with lymph patches; the lateral walls are largely occupied by the openings of the eustachian tubes. The posterior margin of each eustachian tube forms a prominent projection (torus tubarius) which is the inner extremity of the cartilaginous part of the eustachian tube. Between the posterior margin of the tubular orifice and the posterior wall of the nasopharynx lies the lateral pharyngeal recess or fossa of Rosenmüller. The anterior wall is formed largely by the choanae leading directly into the nasal fossae, while the floor is formed partly by the dorsal aspect of the soft palate.

The predilection of neoplasms for certain parts of the nasopharynx together with the special anatomic relations in this area account for much that is curious in the natural history of tumors of this region. The walls of the nasopharynx will not long confine a rapidly growing neoplasm which will soon spread to the adjacent oropharynx and nasal cavities. Those tumors, which spread chiefly by infiltration of neighboring regions, frequently extend to the cranial cavity, the orbit, or the parapharyngeal spaces. Metastatic spread to cervical nodes is common in nearly all types of nasopharyngeal cancer.

The important anatomic features concerned with the spread of nasopharyngeal cancer include the pharyngeal fascia, the relationships of the fossa of Rosenmüller, and the lymphatic drainage of the nasopharynx.

The Fascia

The pharyngeal fascia comprises the *pharyngobasilar fascia,* which is submucosal and is situated within the confines of the muscular walls of the pharynx, and the pharyngeal portion of the *buccopharyngeal fascia,* which is external or peripharyngeal. At the upper border of the superior constrictor muscle the two fascial layers fuse to form a single, dense, fibrous lamina which occupies the sinus of Morgagni. Below, the eustachian tube and the levator and tensor muscles of the soft palate lie between these two fascial layers. External to the buccopharyngeal fascia, the parapharyngeal space separates the pharynx from the mandible, parotid gland, and muscles of mastication. The fascial planes permit mobility of the eustachian tube and pharyngeal musculature, give support and direction to the

Continued

pharyngeal vessels, and form channels for the passage of tissue fluid and lymph.

A neoplastic process may follow these fascial planes; however, this is unusual. More commonly the lesion crosses this fascial barrier and invades the parapharyngeal space, which can be subdivided into three compartments. The prestyloid compartment comprises that portion anterior to the styloid process of the temporal bone and is bounded superiorly by the base of the skull, inferiorly by the submaxillary gland, and posterolaterally by the angle of the mandible and parotid gland. Within this compartment lie the internal maxillary artery, the lingual nerve, and the mandibular division of the trigeminal nerve. Invasion of the prestyloid compartment produces sensory disturbances in the areas supplied by the mandibular and lingual nerves, trismus if the pterygoid muscles are invaded, and depression of the soft palate if its muscles are involved. Upward extension in this compartment leads to intracranial invasion via the foramen ovale, foramen spinosum, or wing of the sphenoid bone. Posterolateral spread may involve the parotid gland with a resultant facial weakness or paralysis.

Posterior to the styloid process, the retrostyloid compartment contains the carotid artery, internal jugular vein, last four cranial nerves, and cervical portion of the sympathetic trunk. The clinical picture seen with invasion of this compartment includes Horner's syndrome and hemiparalysis of the soft palate, lateral pharyngeal wall, tongue, and larynx as well as sensory disturbances in these regions.

Behind the posterior wall of the pharynx and medial to the carotid sheath lies the retropharyngeal compartment. Few symptoms are produced by invasion of this space, although enlargement of the contained lymph nodes may cause compression of the carotid sheath with its contents and produce symptoms not unlike those seen with involvement of the retrostyloid compartment.

The Fossa of Rosenmüller

This fossa is a common site of cancer formation. Because of the local anatomic relationships cancer of this area has an opportunity for spread that is especially important. Dissemination laterally and posteriorly involves the prestyloid and retrostyloid regions and produces clinical evidence of involvement of the parapharyngeal space. Perhaps the most serious route of dissemination is superiorly through the base of the skull into the middle cranial fossa. The foramen lacerum is the most common point of entry, with or without invasion of the surrounding bony structures. Invasion by this route entails early destruction of the basilar cranial nerves in almost direct proportion to their proximity to the foramen lacerum and immediately adjoining cavernous sinus. Thus, cranial nerves III, IV, V, and VI may be affected jointly by a small lesion involving the cavernous sinus. In more advanced cases with extension along the floor of the middle cranial fossa, there may be involvement of the optic nerve, the orbit, or the anterior cranial fossa. Extension to the posterior fossa is rare, although possible. Other less common routes include an anterior dissemination to involve the nasal cavity, sinuses, and orbit.

The Lymphatic Drainage

Involvement of the regional lymph nodes is even more common than cranial nerve complications. Metastases may be bilateral in as many as 40% of the cases. As far as the clinician is concerned the most commonly involved nodes are the upper deep cervical nodes. The superior group is the most important, especially the jugulodigastric node and the nodes beneath the upper end of the sternocleidomastoid muscle. Less commonly involved are the nodes along the spinal accessory nerve and those associated with the transverse cervical vessels. It is unusual to see involvement of nodes in the anterior cervical triangle unless the tumor invades the oropharynx or parapharyngeal space or involves the floor of the nasopharynx. Distant metastases have been reported to the thorax, skeleton, central nervous system, and viscera but these are uncommon.

Symptoms

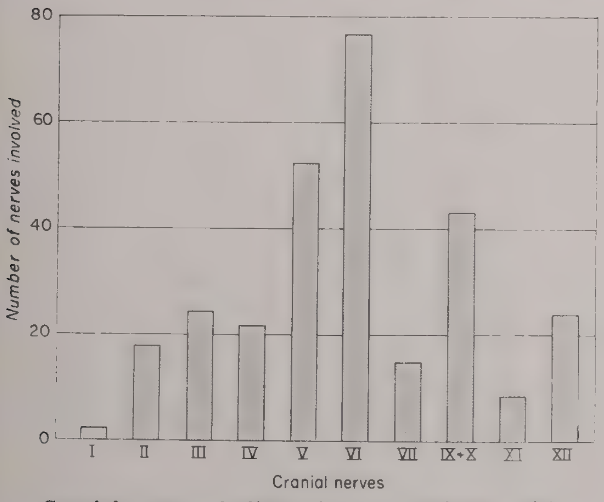
In a recent study,[1] 84% of the patients had generalized symptoms while 16% had primary neurologic complaints.

General Complaints

The most common general complaint was head and face pain, comprising 45% of the presenting complaints. This was nearly always unilateral, frequently with nocturnal exacerbations, and at times suggestive of a trigeminal neuralgia. Thirty per cent had otologic symptoms, including hearing loss, tinnitus, or a feeling of fullness or pressure in the ear. These symptoms nearly always resulted from a unilateral serous otitis media secondary to eustachian tube obstruction in the nasopharynx. Although glandular swelling in the neck was obvious on the initial examination in 70% of the patients, it was the major complaint in only 18% of them. Even less common (15%) were nasal symptoms including obstruction, postnasal discharge, and epistaxis.

Neurologic Complaints

The Figure gives the incidence of involvement of individual cranial nerves in a series of 286 cranial nerve lesions occurring in 111 patients with malignant lesions in the nasopharynx. Most commonly affected were the motor nerves of the eye and the trigeminal nerve. These are involved in what may be termed the petrosphenoidal syndrome. This syndrome is found with intracranial tumor extension via the foramen lacerum. In this region the trunks of cranial nerves II through VI are closely grouped and vulnerable to neoplastic invasion. The patient is ultimately left with a paralyzed, blind eye.



Cranial nerve findings in 111 patients with nasopharyngeal malignant tumors.
(From Thomas, J. E., and Waltz, A. G.: Neurological Manifestations of Nasopharyngeal Malignant Tumors. JAMA 192:95, 1965. By permission of the publisher.)

Pathways of Extension

Although there is no direct communication between the nasopharynx and the orbit, there are several pathways by which a neoplasm may reach the orbit. The first is intracranial extension via the superior orbital fissure. The other routes are extracranial, either by way of the inferior orbital fissure or the nasal fossa. Once the tumor has reached the nasal fossa it may continue toward the orbit either through the sphenopalatine foramen or by direct invasion through the ethmoidal air cells, which are poor barriers to neoplastic spread. Proptosis may occur, therefore, with or without paralysis of the oculomotor nerves. If the motor nerves to the eye are involved intracranially, the paralysis precedes the proptosis. If they are involved extracranially, the paralysis follows the proptosis.

Other cranial nerves may be affected as shown in the Figure. The olfactory nerve is perhaps the least often affected; nerves VII and VIII are only rarely involved. Although the last four cranial nerves lie some distance from the primary site, they are not infrequently involved extracranially.

The combination of cranial nerve defects most commonly found[1] was that involving nerves V and VI. Next in frequency was dysfunction of nerves IX, X, and XII. Several other combinations were observed less frequently and, in addition, there was a wide variety of cranial nerve lesions which followed no particular pattern. There are many eponymous syndromes relating to various combinations of cranial nerve lesions (Table 1), any of which may be seen with nasopharyngeal malignancy.

Pathology

Lack of agreement in classification, especially of the poorly differentiated tumors, renders comparative morbidity statistics unreliable. Histologically, the epithelium of the upper part of the nasopharynx is a pseudostratified, ciliated, columnar type with many goblet cells. Because of the character of the mucous membrane and its associated lymph-

Continued

TABLE 1

Cranial Nerve Syndromes Related to Nasopharyngeal Tumors

Syndrome	Area Involved	Affected Cranial Nerves
Gradenigo's triad	Petrous apex	V, VI + petrositis
Foix syndrome	Ext. wall, cavernous sinus	III, IV, V, VI
Jacod's triad	Petrosphenoidal	II, III, IV, V, VI
Avellis' syndrome	Hemiparalysis of palate and larynx	X
Schmidt's syndrome		X, XI
Hughlings-Jackson syndrome		X, XI, XII
Vernet's syndrome	Jugular foramen	IX, X, XI
Collet-Sicard syndrome	Jugular and posterior condylar foramina	IX, X, XI, XII
Villaret's syndrome	Posterior retroparotid space	IX, X, XI, XII, + sympathetic
Garcin's syndrome	Unilateral paralysis of all cranial nerves	I to XII inclusive
Tapia's syndrome	Hemiparalysis of larynx and tongue	X + XII
Trotter's triad	Ipsilateral temporofacial neuralgia, palatal paralysis, and deafness	V + X

Modified from Godtfredsen, Erik: Ophthalmologic and Neurologic Symptoms at Malignant Nasopharyngeal Tumours: A Clinical Study Comprising 454 Cases; With Special Reference to Histopathology and the Possibility of Earlier Recognition, Copenhagen, Einar Munksgaard, 1944.

TABLE 2

Classification of Malignant Tumors of the Nasopharynx

Subdivision	Remarks	Incidence (%)
Squamous cell carcinoma	Includes all degrees of squamous differentiation (grade 1 to grade 4)	19
Lymphoepithelioma	Includes all undifferentiated carcinomas whether lympho-epithelioma or transitional cell type	67
Lymphosarcoma		5
Others	Miscellaneous types including small cell, cylindroma, etc.	9

Modified from Scanlon, P. W.; Devine, K. D., and Woolner, L. B.: Malignant Lesions of the Nasopharynx, Ann Otol Rhin Laryng 67:1005, 1958.

oid and glandular structures, many different histologic varieties of tumor may be found. Table 2 gives the pathologic classification and incidence of malignancies of the nasopharynx from a Mayo Clinic study reported by Scanlon and co-workers.[2] Apart from the squamous-cell carcinomas of various grades, the presence of lymphoid tissue may give rise to lymphoma, while the presence of glandular elements may give rise to adenocarcinoma. In addition, any of the connective tissue sarcomas may be found. Metastatic tumors to the nasopharynx have been reported but are uncommon. Scanlon and co-workers[2] stated that lesions such as juvenile fibromas, chordomas, craniopharyngiomas, and plasmacytomas and, to a lesser extent, teratomas, hemangiomas, lymphangiomas, posterior choanal polyps, tuberculous retropharyngeal lymph nodes, or even pituitary tumors may resemble primary malignant lesions of the nasopharynx so closely that differentiation can be made only on biopsy.

Diagnosis

Every effort must be made to inspect the entire nasopharynx. Topical anesthesia frequently helps to control gagging. Another measure which at times may be useful consists of passing soft rubber catheters through each nostril into the nasopharynx and then back out through the mouth. A gentle tug on the catheters will then retract the soft palate forward and provide a good view of the nasopharynx. Digital examination may be helpful. Often a cotton swab passed over a malignant area will incite surface bleeding. Many examiners become proficient with the nasopharyngoscope, but this requires practice.

Biopsy

Nasopharyngeal biopsy is an extremely important diagnostic procedure. Biopsy of obviously involved or suspicious areas can be readily performed transnasally as an office procedure. Occasionally one encounters a case in which the clinical pattern suggests a nasopharyngeal lesion, but no obviously involved or suspicious site can be found in the nasopharynx. In these instances, multiple blind biopsies under general anesthesia may be successful in locating an elusive primary lesion. This technique is even more valuable if immediate frozen-section pathology reports can be obtained. On occasion, an excision of a metastatically involved cervical node may establish a diagnosis of malignancy; however, it is not recommended that these nodes be excised for biopsy purposes unless all other diagnostic routes have been exhausted.

X-ray Studies

Roentgenographic studies are frequently helpful. A lateral view may show a mass in the nasopharynx or an erosion in the sphenoid area. Perhaps the most important view is the stereoscopic view of the base of the skull, which may show unilateral decalcification in the petrosphenoidal region or enlargement of the foramen lacerum or foramen ovale on one side.

No attempt will be made to list the lesions which may simulate carcinoma of the nasopharynx; such a list would be so extensive as to be meaningless. Practically any single cranial nerve or any combination of cranial nerves as well as the cervical sympathetic nerves may be involved. Therefore, any patient presenting with an unexplained cranial nerve lesion or any of the cranial nerve neuralgias and all patients with a conductive hearing loss (especially unilateral) should undergo examination of the nasopharynx.

Treatment

The treatment of nasopharyngeal carcinoma is largely a radiotherapeutic problem, since operation alone is not curative.

Radiotherapy

Many of the tumors are radiosensitive; therefore, an attempt should be made at curative treatment. Palliative treatment is reserved for recurrent lesions or lesions associated with bilateral fixed nodes or distant metastases. The treatment of choice is supervoltage irradiation, with local radium application being used for localized recurrent lesions. Some institutions use prophylactic irradiation to the cervical regions bilaterally, while others prefer to treat the neck only when metastases are palpable.

Continued

There are certain technical considerations which add difficulty to radiotherapy in this region of the body. The nasopharynx is situated beneath the center of the base of the skull in close relationship with the brain and several of the special sense organs. Lederman[3] has pointed out that, of the related structures, the eye, the cerebrospinal axis, and the salivary glands are susceptible to radiation damage; but the auditory, vestibular, and olfactory organs and the pituitary gland are rarely injured.

Surgery and Irradiation

Recently a combined surgical and irradiation approach has been tried in certain cases of squamous-cell carcinoma with cervical metastases. This consisted of irradiation to the primary lesion with neck dissections where nodes were palpable; if necessary, bilateral radical neck dissections were done. The efficacy of this approach will have to await comparative statistical analysis.

Results of Treatment

Results of various studies indicate a 9.8[4] to 27.6%[5] survival rate. The two most important factors determining salvage rates are the type of the lesion and the extent of dissemination. The five-year survival rates with lymphoepithelioma and lymphosarcoma can be expected to exceed those with squamous-cell carcinoma by two or three to one. The importance of tumor dissemination is emphasized by one study[2] in which the five-year survival rate was 30% when the tumor was confined to the nasopharynx but only 15% when there was extension to regional nodes. The survival rate was 27% when the tumor had advanced superiorly and destroyed the floor of the middle cranial fossa or involved the cranial nerves. There were no five-year survivors when both types of metastatic spread were present. The over-all five-year survival rate was 17% in the series.

There is so much disagreement in classification and in reporting of results that, to date, comparative morbidity statistics are of little value. In an attempt to establish uniformity, a system of classification and staging has been proposed.[6] It is hoped that universal acceptance by clinicians of such a system will enhance cancer control through more accurate collection of data, more accurate evaluation of therapy, and better reporting of results. In this system, the TNM system, "T" refers to the tumor or primary lesion and its extent; "N" refers to regional nodes and their condition; and "M" refers to distant metastases. Each component is then subdivided, with numerical suffixes indicating the extent of involvement (Table 3). The tumors then can be classified into four stages, the essential features of which are summarized in Table 4.

A Stage I lesion is a small growth in the nasopharynx without cervical lymph node involvement or distant metastases. A Stage II lesion is more extensive locally but still without evidence of local or distant spread. The essential feature of a Stage III lesion is the presence of palpable cervical nodes that

TABLE 3

The TNM System of Classification for Carcinoma of the Nasopharynx

Definition of T Categories

T1	Tumor limited to one site in the nasopharynx (vault or lateral wall)
T2	Tumor extending into two sites (vault and lateral wall)
T3	Tumor extending beyond nasopharynx

Definition of N Categories

N0	No clinically palpable nodes
N1	Palpable cervical nodes; not fixed
N2	Palpable cervical nodes; fixed

Definition of M Categories

M0	Distant metastases absent
M1	Distant metastases present

TABLE 4

Summary of Clinical Stages of Carcinoma of the Nasopharynx Based on the TNM System

Stage	T	N	M
I	T1	N0	M0
II	T2 or T3	N0	M0
III	T1, T2, or T3	N1	M0
IV	T1, T2, or T3	N2	M0
		N0, N1, or N2	M1

are not fixed. Any degree of primary involvement may be present in the nasopharynx; however, there is no distant spread. A Stage IV lesion is one in which there are fixed cervical node metastases or distant mestastases or both. It must be emphasized that stage classification is a clinical one and is based on the anatomic extent of the disease at the time of the initial examination. It is intended that stage classification will group together patients who have the same degree of disease and who should have a similar prognosis.

The results of field trials[6] in which 371 carcinomas of the nasopharynx were studied demonstrated that survival of patients with nasopharyngeal carcinoma can be correlated with the proposed stages. There was a 60 to 76% five-year survival with Stage I lesions, 38 to 41% with Stage II, 29 to 34% with Stage III, and only 17 to 25% with Stage IV. At first glance some of these values may seem high when compared with many of the previously reported studies. However, when one considers the insidious nature of the tumors, it must be realized that the majority of the reported series must comprise Stage III or Stage IV lesions. For example, the study by Thomas and Waltz[1] contained only tumors with cranial nerve involvement and these would all have been Stage III or Stage IV. The survival rate in their study was 24%. Likewise, in the study by Scanlon and co-workers[2] the tumors would also have been largely Stage III and Stage IV lesions, and their results show a 17% five-year survival rate.

Summary

Carcinoma of the nasopharynx comprises from 0.3 to 0.4% of all malignant tumors of man. The peak incidence is in the fifth and sixth decades of life, with a male preponderance of approximately 3:1. A variety of histologic cell types can undergo malignant degeneration in this area; perhaps the most common malignancy is lymphoepithelioma. In many instances the point of origin is difficult to determine at the time the tumor is discovered. The fossa of Rosenmüller and the vault are the most commonly affected areas. Tumors of the sarcoma group spread more readily to regional nodes, occur in younger age groups, and are more sensitive to treatment than are tumors of the squamous-cell group.

When the tumor extends through the foramen lacerum, cranial nerves V and VI are most frequently involved. When extension is in a posterolateral direction through the parapharyngeal space, cranial nerves IX, X, XI, and XII and the cervical sympathetic nerve are more commonly affected. However, involvement of any combination of cranial nerves may occur.

The results of treatment are uniformly poor, with a five-year survival rate of less than 25%. The more important features in determining survival are the type of tumor and the extent of spread. While the results are not encouraging, it can be hoped that further refinements in technique, earlier diagnosis, and a better understanding of the biologic variations involved will lead to a significant improvement in the survival rate.

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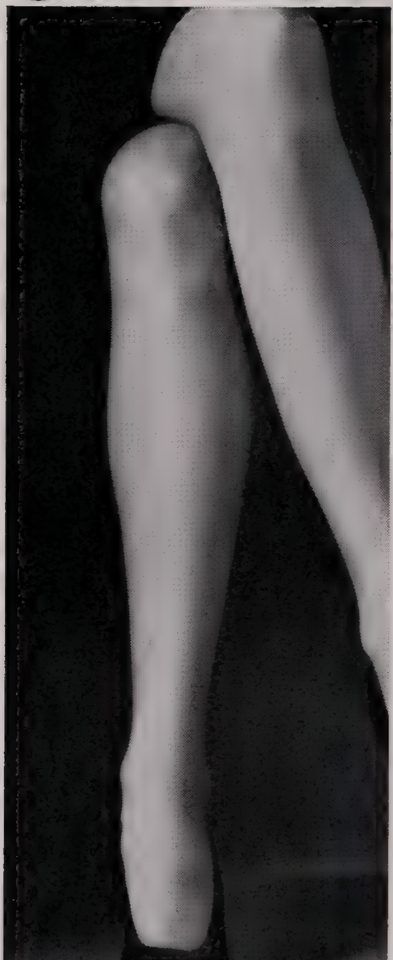

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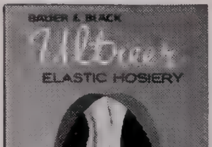

KENDALL
BAUER & BLACK SUPPORTS DIVISION

Clinical Path Conference

Systemic Torulosis in a Diabetic Patient*

This 69-year-old negro female began having episodes of confusion, disorientation and slowness of thought five months prior to admission to Hennepin County General Hospital on August 20, 1963. Recurrent headache, nausea and vomiting had necessitated her admission to a private hospital in early July, 1963. A two-year history of fluctuating cervical adenopathy was elicited, and a scalene node biopsy was reported as showing noncaseating epithelioid granulomata. Thereafter, the patient became somnolent and was noted to have a stiff neck. No seizures or syncopal episodes were reported; however, the family physician was said to have suspected a brain tumor.

There was a 12-year history of adult type diabetes mellitus treated with 25 units of NPH insulin. The diabetic state had been well controlled until recent weeks when the patient's fluid and food intake diminished, and a 15-pound weight loss had occurred.

The onset of deep coma led to her transfer to Hennepin County General Hospital. When the patient was given an infusion of 300 cc. of 10% dextrose in water and promptly awakened, the possibility of a hypoglycemic reaction was considered. Her blood sugar was reported to be 129 mg.%.

Physical Examination

The patient appeared as a confused, lethargic, combative, elderly negro female. Her verbal responses to questions were inappropriate, and she was markedly disoriented. The blood pressure was 170/90 mm. of mercury; the pulse 90 per minute; the respiratory rate 18 per minute, and the temperature 100° F. Optic fundi showed no evidence of papilledema. Slight nuchal rigidity could be demonstrated. The lung fields were clear to percussion and auscultation. A Grade II systolic murmur was present at the cardiac apex. The abdomen was soft and doughy, and did not appear to be distended. The liver, spleen, and kidneys were not enlarged to palpation. The bowel sounds were not accentuated. Costovertebral angles were nontender. The turgor of the skin suggested severe dehydration. Neurological examination showed decreased sensation on the left side of the body as tested by pinprick. The deep tendon reflexes were slightly enhanced on the

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*See Test Your Word Score Page 607.

Continued

left. Bilateral Babinski toe signs were present, the right being more marked than the left.

Laboratory Studies

The hemoglobin was 11.1 grams %; the white blood cell count was 10,100 per cu. mm. with 88% neutrophils and 12% lymphocytes. Urinalysis revealed a specific gravity of 1.015 with 4+ glycosuria and no proteinuria. Microscopic examination of the urinary sediment showed occasional red blood cells and pus cells. A urine culture grew out greater than 100,000 colonies per cc. of proteus species and gamma streptococci. A sputum culture showed a mixed flora consisting of pseudomonas, proteus, E coli and Klebsiella species. The erythrocyte sedimentation rate was 121 mm. per hour (Westergren). A BUN was 14 mg.%. The serum sodium was 131 mEq/L; the serum potassium 4.2 mEq/L; the serum chloride 86 mEq/L; and the CO_2 combining power 26 mEq/L. Stool guaiac tests were weakly positive. The blood VDRL was positive only with undiluted serum, and the blood Hinton test was 3+. The Reiter protein complement fixation test was non-reactive. Tests of dermal sensitivity with coccidioidin, blastomycin and histoplasmin were non-reactive in 48 hours. A 1:10,000 Mantoux test was negative.

Lumbar Puncture

Shortly after admission, the patient's neurologic status further deteriorated. On lumbar puncture, the spinal fluid was slightly turbid and revealed a cell count of 62 per cu. mm. with 86% mononuclears. The spinal fluid protein was 33 mg.% and the sugar 100 mg.%. The colloid gold curve was reported as 1 4 4 3 3 2 1 0 0 0. Budding yeast-like organisms were demonstrated in the spinal fluid on an India ink preparation. Spinal fluid culture revealed Cryptococcus neoformans. The EEG was abnormal, showing diffuse slowing of rhythm.

Progress

The patient was begun on Amphotericin B, 50 mg. daily, given intravenously to run over a period of two to six hours. Her sensorium and neurologic status deteriorated rather rapidly during her hospital course. Therapy was instituted with penicillin and Kanamycin because of a left lower lobe pneumonia. The serum calcium was 8.4 mg.% and the serum phosphorus 2.2 mg.%. Serum alkaline phosphatase was 6.5 KA units. The blood sugars fluctuated between 330 and 540 mg.%, and the CO_2 combining power ranged from 19 to 23 mEq/L. The total serum proteins were 6.5 grams % with a serum albumin of 3.6 grams % and a serum globulin of 2.9 grams %. A serum electrophoresis was normal. On several occasions, coffee-ground-like material was aspirated after tube feedings. The hemoglobin fell to 7.5 grams %, and the peripheral blood smear showed marked microcytosis.

Intrathecal administration of Amphotericin B in a dosage of 0.5 mg. with 20 mg. of hydrocortisone was instituted every other day. The cerebrospinal fluid pressure was 400 mg. of mercury. Right-sided seizures involving the upper and lower extremity with tonic and clonic movements supervened. Decadron 16 mg. daily was given in an effort to reduce cerebrospinal fluid pressure. The BUN rose to 45 mg. % with a creatinine of 2.5 mg.%. The patient remained in deep coma and developed a marked febrile response up to 105° F. A chest x-ray showed an acute infiltration in the right midlung field and a pathologic fracture of the distal third of the left clavicle. Chloromycetin and penicillin were administered intravenously; the patient's fever lysed to hypothermic levels. There was a marked increase in seizure activity in spite of 300 mg. of Dilantin daily. With progression of the right lower lobe pneumonia and the onset of shock, the patient expired. The total dosage of Amphotericin B was approximately 700 mg. intravenously and 10 mg. intrathecally.

Discussion

Dr. Horace Zinneman*

This elderly, colored diabetic female developed signs and symptoms of an intracranial process which was clearly of some months' duration. Later in the protocol, we see that these symptoms were manifestations of a yeast infection of the central nervous system, since Cryptococcus neoformans was cultured from the cerebrospinal fluid. However, we must also consider the possibility of a disseminated cryptococcal infection. Also we must ask: is the cryptococcal infection secondary to some other disease process known to predispose the individual to a deep mycosis? Certainly Hodgkin's disease rates foremost in one's consideration as the primary disease in which Cryptococcus is a secondary invader. Lymphosarcoma, acute leukemia, tuberculosis, sarcoidosis, and certain neoplastic diseases may also coexist with cryptococcosis. More recently, pulmonary alveolar proteinosis has been implicated as one of the associated diseases.

A history of fluctuating cervical adenopathy was obtained, and a scalene node biopsy showed non-caseating epithelioid granulomata. Now this can mean many things. Classically, this is sarcoidosis. However, we still do not know what sarcoidosis is, since the same histologic picture may be present in infections with Mycobacteria and certain fungi.

Addisonian Crisis

I do not know why this patient promptly awakened after an infusion of 300 cc. of 10% dextrose. Certainly hypoglycemia was not present. One thinks immediately of an Addisonian crisis, but the patient's blood sugar and electrolyte studies do not confirm this diagnosis. Adrenal destruction and adrenal insufficiency are known to occur in the systemic deep mycoses. A recent Mayo Clinic review reported adrenal involvement in three of nine cases of disseminated cryptococcal disease.[1] These investigators also recognized that infections with Histoplasma capsulatum frequently terminated in adrenal destruction.

Physical Examination

The patient did have a temperature when she arrived at this hospital in a comatose state. She did not have papilledema. A Grade II systolic murmur was present, and it might be interesting to know whether she always had that murmur or whether we are dealing with a new murmur. In the latter instance, we might consider the presence of a fungal endocarditis due to Cryptococcus neoformans. The neurological findings suggested bilat-

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Continued

eral cerebral disease with the majority of her cerebral damage on the right side.

Laboratory Studies

The hemoglobin of 11.1 grams % is a little low for a post-menopausal woman. An erythrocyte sedimentation rate of 121 mm. per hour is also excessive for cryptococcal infection alone. These findings should alert us to the possibility of an underlying disease process. Urinalysis showed significant glycosuria as well as a urinary tract infection. I would venture to guess that we might have cultured Cryptococcus neoformans from the urine, as the organism is present in the urine in about 30% of cases. A urine culture for fungi should be part of our work-up in any suspected case of cryptococcosis.

Positive Serology

Since the Reiter protein complement fixation test was non-reactive, I think the positive serology most likely represents a biologic false positive. A false positive test for syphilis occurs in malaria, infectious mononucleosis and almost routinely after smallpox vaccination. Some neoplastic diseases, such as malignant lymphoma and particularly multiple myeloma, may be associated with similar findings. This bears no relationship to the cryptococcal infection as far as I am concerned.

Lumbar Puncture

A lumbar puncture was performed and showed yeast-like organisms. This is important. A cerebrospinal fluid sugar was 100 mg. %, which is rather high when we have a cell count of 62 per cu. mm. This finding may reflect intravenous feeding or the diabetic state. It suffices to call attention to the fact that when you have a significantly elevated white cell count in the spinal fluid, the sugar is metabolized to a low level by the leukocytes. Cryptococcus neoformans is easily identified on an India ink preparation and by culture. I wonder if we could see the x-ray films at this time?

Radiologic Findings

Dr. Shih Hao Tsai*

An admission chest x-ray revealed calcification around the arch of the aorta and in the hilar areas with diffuse accentuation of lung markings bilaterally. A faint nodular density was present in the left upper lung field and interpreted as a granuloma. Skull x-rays revealed multiple radiolucent lytic defects throughout the calvarium. The skull defects were somewhat rounded in appearance, and many were of similar size. In the occipital region of the skull, there were several larger defects thought to represent confluence of smaller lytic lesions. These skull defects were most suggestive of either multiple myeloma or metastatic carcinoma. An x-ray survey of the pelvis and spine was normal.

Here is a follow-up chest x-ray taken three days prior to death. A slight pleural effusion is present at the right base together with some infiltration in the right upper lobe which could represent either active pneumonia or a pulmonary infarction. The interesting thing here is the fracture of the distal third of the left clavicle. There is a radiolucent area at the fracture site, and this most likely represents a pathological fracture.

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*Chief of the Radiology Service, Hennepin County General Hospital.

Dr. Horace Zinneman

Thank you, Dr. Tsai. I notice the bony defects in the skull are quite striking in that they are completely free of osteoblastic reaction at the periphery. Now, how do these defects of bone fit with a cryptococcal infection? We know that bony defects do occur in about 10% of cases of cryptococcal infection. The lesions are lytic with very little periosteal reaction and represent cryptococcal osteomyelitis. Swelling is frequently present at the site, and they are clinically tender to palpation. Bone lesions can occur in almost any bone, but particularly long bones, pelvis, ribs and clavicles. I know of no report that Cryptococcus neoformans causes punched out lesions in the skull. That would be very unusual. This is another point that suggests the cryptococcal infection is secondary to another disease state. Dr. Tsai thought he might suggest either multiple myeloma or metastatic carcinoma. Sarcoidosis could present with bony defects, but these more often occur in the terminal phalanges of the hands.

The patient's course was characterized by recurrent episodes of pulmonary infiltration. We know that the portal of entry of Cryptococcus is almost uniformly the lung. The pneumonitis could be due to Cryptococcus neoformans. A bacterial etiology seems more likely, however. The yeast infection of the central nervous system must be treated with Amphotericin B.

Therapy

It is generally advisable to begin intravenous Amphotericin B therapy at about 0.25 mg. per kilogram and increase the daily dosage to about 1.0 mg. per kilogram of body weight. An initial course of intravenous therapy consists of a total dose of two to four grams. Almost uniformly, one has to give a second course of therapy. Amphotericin B is a toxic drug, and many side effects are encountered. The patients become weak and complain of muscle pain, chills, and pain at the site of infusion. Nausea and vomiting are quite often encountered but can be alleviated with chloropromazine. Thrombophlebitis can be minimized by threading an intercath up the arm to the level of the axillary vein where there is a larger volume of blood and the drug is sufficiently diluted. If we give enough Amphotericin B intravenously, we always see a rather severe anemia due to bone-marrow depression. Similarly, the renal toxicity is cumulative once a total dose of 7 to 10 grams is exceeded. Pathologically, one sees irreversible glomerular and tubular damage with renal calcification. The therapeutic aim should be to treat the patient with a total drug dosage of under 7 grams.

In view of the patient's rapid deterioration, intrathecal Amphotericin B was surely indicated. It is customary to begin with 0.1 mg. and gradually work up to 0.5 mg. in each intrathecal injection. The addition of hydrocortisone helps circumvent the majority of the adverse reactions to therapy. One should administer the drug every other day, since Amphotericin B can be detected for about 48 hours after injection into the subarachnoid space. As Cryptococci are said to be sensitive to .03 mg. per ml., we need not give massive doses. Therapeutic complications, particularly dry arachnoiditis and paraplegia, have occurred in a few instances. For this reason I would not like to give more than 0.5 mg. in a single injection intrathecally.

The Ommaya reservoir has recently been described in the literature.[2]

Continued

This device consists of an indwelling subcutaneous capsule made of silicone rubber which fits into a cranial burr hole and is connected to a ventricular catheter. Amphotericin B is diluted and injected into the capsule and pumped into the ventricle periodically. I have had no experience with this technique. Certainly the principle of having the Amphotericin B diluted as it reaches the cerebrospinal fluid is well served. Let us remember that Amphotericin B is not an aqueous solution; it is a colloidal suspension. A new drug, Hamycin, has shown promise in experimental cryptococcosis in animals. This agent is soluble in methanolic calcium chloride. It is reported to eradicate Cryptococci from mouse brain, which is truly remarkable. Very impressive blood levels are easily obtained with Hamycin as well. We may see Amphotericin B replaced with Hamycin in the near future.

Multiple Myeloma

Now I want to go over a few things which have made me think of another condition. First of all, the hemoglobin fell to 7.5 grams % with no evidence of external bleeding. The marked elevation of the sedimentation rate is of interest here. Both of these parameters suggest an underlying malignant process. A biologic false positive serology may occur in multiple myeloma. The radiolucent defects in the skull and pathologic fracture of the clavicle suggest multiple myeloma. Similarly, recurrent pneumococcal pneumonias are the hallmark of the disease. As you know, multiple myeloma is often associated with an immunologic defect characterized by a functional agammaglobulinemia. Patients frequently have a very high serum peak which resembles gammaglobulin, but is not truly gammaglobulin. It is an immunologically inactive globulin related to gammaglobulin. The normal serum electrophoresis observed in this patient is evidence against the diagnosis of multiple myeloma. However, not all cases of multiple myeloma have the typical serum pattern of a slender, sharply circumscribed homogeneous serum peak. About 20% of all myelomas have a normal serum pattern and excrete Bence Jones proteins in the urine. Approximately 50% of all myelomas have Bence Jones proteins in the urine. Initially the proteins are in the serum, but this protein is a small molecule which readily passes through the glomerular filter and is found in the urine. Bence Jones protein is nothing more than the light chain of the gammaglobulin with a molecular weight of about 30 to 35,000. Whenever there is any reasonable suspicion of multiple myeloma, I insist on an electrophoresis of the urine and the serum. I say an electrophoresis because the standard test of Bence Jones protein, namely, acidification and boiling, is not too reliable in most hands. First of all, if you have just a little turbidity in the urine, it may be overlooked upon heating. Secondly, each Bence Jones protein has its own optimal pH for maximal precipitation. If the urine is tested at pH_5, most Bence Jones protein would show at least minimal precipitation. I don't know how many laboratories adjust their pH exactly to five. In most hospitals the determination of Bence Jones proteins is not a very reliable procedure, particularly since the albumin test strip has been used for routine urinalysis.

Initially, we do not think of multiple myeloma in this case. There was no abnormal serum peak on electrophoresis and no reversed albumin-globulin ratio. However, I am assuming this case fits into the 20% of cases which have perfectly normal serum electrophoresis with Bence Jones proteinuria. Multiple myeloma is not one of the usual underlying diseases for cryptococcosis. Nonetheless, you can see that I am taken with the possibility of multiple myeloma having given her anemia, bony defects, pathologic fractures, recurrent pneumonias, and an immunologic defect which might have facilitated the development of cryptococcosis.

Clinical Diagnosis:

Disseminated cryptococcosis
Multiple myeloma

Pathology

Dr. Robert L. Strom*

I would like to congratulate the laboratory for shedding the initial light on this diagnostic problem. The spinal fluid examination was of paramount importance in this case. A low cell count with mononuclear predominance is the rule in cryptococcosis. The absence of stainable bacteria and a minimal depression of cerebrospinal fluid sugar should alert the technologist to this diagnosis. Cryptococci are easily mistaken for lymphocytes or red blood cells on a spinal fluid counting chamber. An India ink preparation reveals budding yeast five to 15 micra in diameter with clearly defined capsules.

Cryptococcus neoformans is easily cultured on Sabourauds dextrose agar at room temperature. Non-pathogenic strains of cryptococci are excluded by demonstrating growth at 37° C on blood agar. A positive urease test helps distinguish the yeast colony of Cryptococcus neoformans from Candida species.

Post-Mortem Examination

The post-mortem examination in this case revealed several interesting findings. Both of the patient's lungs weighed in excess of 500 grams. A granuloma measuring approximately 1½ cm. in diameter was present in the left upper lobe of the lung. The lesion showed central caseation and fibrosis at the periphery with a marginal infiltration of lymphocytes and occasional multinucleated giant cells. Small adjacent areas of fibronodular infiltrate were seen in a subpleural location containing similar giant cells. On closer observation, the giant cells contained no demonstrable Cryptococci on routine hematoxylin and eosin stain (Figure 1). These foci in the lung apparently represent the portal of entry of the Cryptococcus neoformans. An active pneumonitis was present in the lung at the time of death and was the cause of the terminal infectious episode. The acute exudative reaction was most consistent with a pneumococcal pneumonia of a few days' duration.

The hilar lymph nodes were markedly enlarged and caseous. Microscopically, giant cells were seen in a background of loose pink collagen. The giant cells were frequently in a perineurial location, and some of them appeared to contain intracytoplasmic inclusions. The inclusions seen were of two general types and are illustrated in Figure 2. The giant cell in the upper right quadrant contains spherical clear areas within the cytoplasm which on hematoxylin and eosin stain strongly suggested ingested yeast organisms. I was unable to verify the presence of ingested organisms with Gomori methenamine-silver, Gridley or Mayer's mucicarmine stains. The

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*Associate Pathologist and Director of Bacteriology Laboratory, Hennepin County General Hospital.

Continued

second large giant cell in the lower left quadrant (Figure 2) contains an asteroid. Asteroids are frequently described in sarcoidosis but are known to occur in other granulomas.

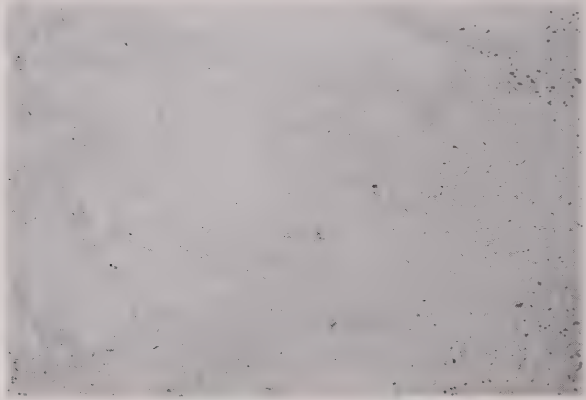

Fig. 1 — Fibronodular area from lung portal of entry showing giant cells and scarring. Hematoxylin and eosin x40.

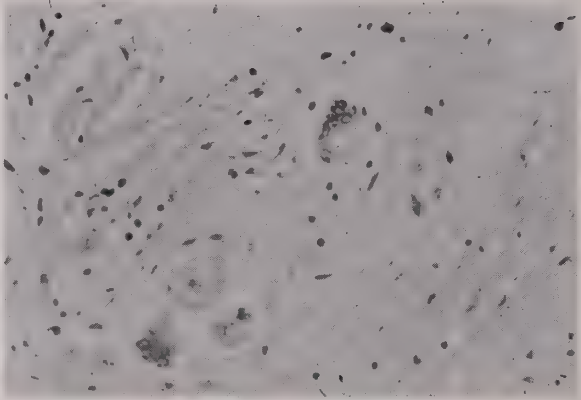

Fig. 2 — Giant cells from hilar area with intracytoplasmic inclusions. Hematoxylin and eosin x100.

At this point it is interesting to speculate about the diagnosis of noncaseating epithelioid granulomata in the cervical lymph nodes removed several months previously. Did these lymph nodes represent sarcoidosis or possibly a granulomatous reaction to Cryptococcus neoformans? Recently Harris et al.[3] have emphasized that cryptococcosis may occur in the presence of sarcoidosis. The absence of epithelioid granulomata and Schauman bodies in the hilar lymph nodes is evidence against sarcoidosis. Caseation necrosis favors progressive pulmonary cryptococcosis.

The spleen was not enlarged; it weighed 110 grams. The architecture was grossly abnormal, being replaced with granulomatous change. Intracytoplasmic inclusions were again seen in giant cells in the red pulp of the spleen (Figure 3). A solitary healed granuloma was seen in the section of liver I had available for study.

The renal tubules showed uniform necrosis with some foci of calcification in the tubular epithelium. These findings were consistent with toxic changes occurring during Amphotericin B administration. Several smaller renal arterioles were hyalinized, suggesting long-standing diabetes.

On studying the skull defects we found no evidence of multiple myeloma.

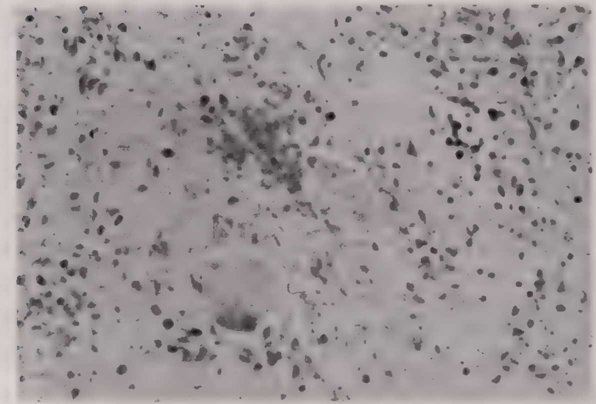

Fig. 3 — Giant cells from granuloma in spleen. Hematoxylin and eosin x100.

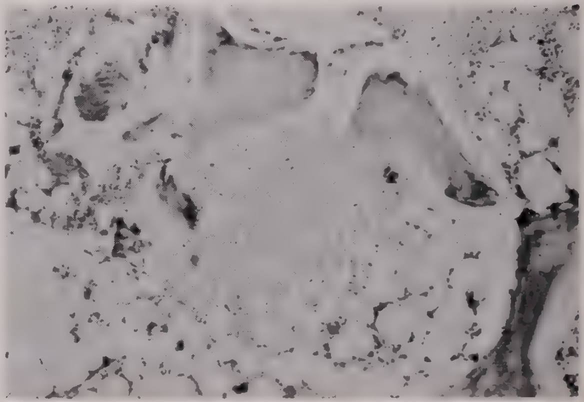

Fig. 4 — Granulomata in normal bone marrow from lytic lesions of the skull. Hematoxylin and eosin x40.

Bone marrow elements between the trabeculae showed a normal cellularity. Discrete epithelioid granulomata were seen within the marrow spaces eliciting a fibrous response and destroying adjacent bone (Figure 4). Large giant cells were present in a background of fibroblasts with a few accompanying lymphocytes and plasma cells. No stainable organisms could be demonstrated in the skull lesions. Such lytic skull lesions are unusual in either sarcoidosis or cryptococcosis.

A white cloudy exudate was present over the dorsal convexities and at the base of the brain. Coronal sections through the cerebral hemispheres revealed striking changes (Figure 5), consisting of grayish-white exudate deep within many of the sulci of all lobes of both hemispheres. Areas of softening were most voluminous in occipital sulci. The deeper cerebral structures appeared uninvolved for the most part. Although arachnoiditis and secondary hydrocephalus may occur in central nervous system cryptococcosis, there was no evidence of ventricular enlargement in this case.

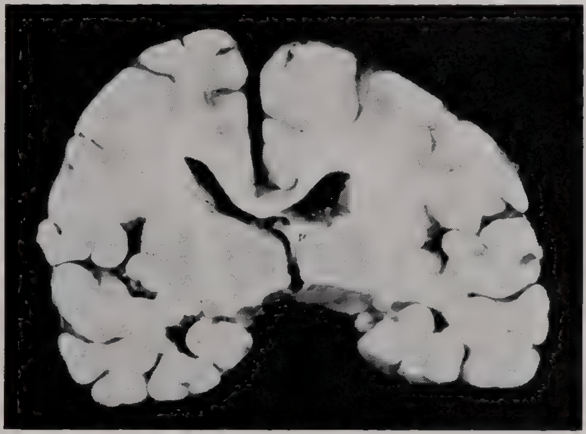

Fig. 5 — Coronal section of brain showing grayish white exudate in many cerebral sulci.

Fig. 6 — Budding organisms of Cryptococcus neoformans in brain tissue. Hematoxylin and eosin x100.

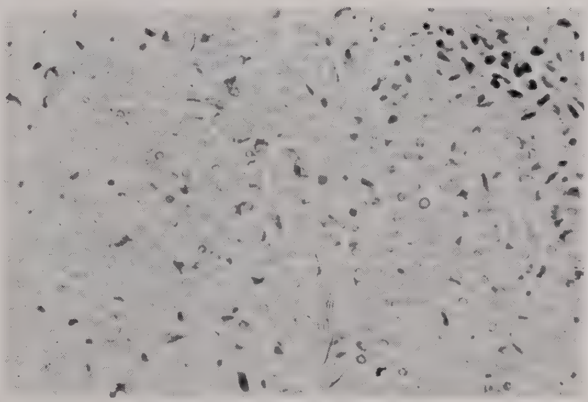

Fig. 7 — Mayer's mucicarmine stain of Cryptococcus neoformans in brain tissue. x100.

Microscopic examination of the areas of softening along the sulci showed an inflammatory process extending along the meninges and into the brain substance adjacent to cerebral vessels. Cryptococcus neoformans organisms were readily recognizable in large numbers on hematoxylin and eosin stains (Figure 6). In some areas the yeast cells were seen to bud in a characteristic fashion. When the sections were stained with Mayer's muci-

Continued

carmine technique, the organisms stood out more prominently and exhibited a reddish-pink hue (Figure 7).

We may conclude that this elderly diabetic patient has suffered a hematogenous dissemination of Cryptococcus neoformans from a primary lung focus with involvement of the brain, bones, lymph nodes and internal organs. Diabetes mellitus has been considered by some investigators to be a predisposing condition which may well have altered the patient's innate resistance. In view of the absence of stainable organisms in many of the body tissues, one may speculate on the presence of associated sarcoidosis. The lytic bone lesions particularly in the skull were indeed an unusual manifestation.

Pathological Diagnosis:

1. Disseminated cryptococcosis
2. Diabetes mellitus
3. Renal tubular necrosis due to Amphotericin B therapy

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Hennepin County General Hospital

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*Director of Bacteriology Laboratory.

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The most important duty of the physician is to prevent illness.

Most patients get better without much help from the physician by the power of nature.

Employ only one medicine at a time in all your cases and note its effects carefully.

Never speak unfavorably of other physicians. Every one of us has his lucky and unlucky hours.

— Isaac Ben Soliman (9th century)

The Superior Man — Confucius (551-479 B.C.)

The superior man is always candid and at ease with himself or others; the inferior man is always worried about something.

Tolerance

Unfortunately I have an open mind. I let down a window in my brain about six or seven inches from the top even in the bitterest weather.

— Heywood Broun

Derivatively Speaking

Clinic — from Greek *klinikos* (pertaining to a bed)

Grand Rounds

Heart Disease of Obscure Etiology in the Alcoholic*

IN A GENERAL hospital practice one not infrequently encounters a patient who has manifestations of heart disease with no readily apparent cause. It may come to attention because an incidental chest x-ray shows cardiomegaly, because a patient has an unexplained attack of pulmonary edema, because of a complaint of breathlessness on exertion or because an examination shows a well developed picture of right-sided heart failure. In an attempt to establish the etiology one reviews the common causes of heart failure. *Coronary artery disease,* being one of the more common causes, is considered but dismissed since, although the patient may have some complaints of precordial discomfort during the process of his disease or some nonspecific abnormality on his electrocardiogram, he does not have a clear-cut story of a previous myocardial infarction, a history of angina pectoris, or an electrocardiogram which shows a definite myocardial infarction pattern. *Hypertensive cardiovascular disease,* another common cause of heart failure, is not a satisfactory explanation because, although hypertension may be present during overt heart failure, the blood pressure is not elevated when the heart failure is compensated. Also the stigmata of hypertensive disease — hypertensive retinopathy, renal failure or electrocardiographic evidence for left ventricular hypertrophy — are absent. Valvular disease cannot be incriminated because of the absence of murmurs, though a systolic murmur may be present when the patient is in failure. *Cor pulmonale* is often incriminated, but the presence of unexplained left ventricular enlargement, mild clinical signs of emphysema, and the equivocal pulmonary function studies make this explanation unlikely. Occult congenital heart defects that may survive to middle adult life, such as an atrial septal defect or Eisenmenger's complex with balanced shunts, are infrequently found. One then turns to the well described uncommon causes of heart failure for an explanation.

Heart disease caused by a toxic or invasive infectious process as in bacterial endocarditis, pneumococcal pneumonia, meningococcal septicemia, diphtheria or acute rheumatic fever is usually obvious from the other

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*Medical Grand Rounds, Hennepin County General Hospital, January 4, 1966.

Continued

clinical manifestations of the primary disease. The same may be said of the heart disease that complicates the collagen or endocrine disorders, the infiltrative cardiomyopathies and progressive neuromuscular dystrophy. When these possibilities have been exhausted and the cause of the heart disease remains unexplained, the clinician may follow one of two courses: he may call the heart disease arteriosclerotic in origin and be satisfied with rather nebulous criteria for this diagnosis, or he may call it cardiac disease of unknown origin. The former course provides some degree of ego satisfaction in assuming to know the cause, but the latter offers the excitement of an exploration into the area of cardiomyopathy of obscure etiology.[1,2,3,4,5]

I would like to discuss two forms of cardiac failure that may be seen in the alcoholic. The first, beriberi heart disease, is a well described clinical and biochemical defect which has been appreciated since 1930. The latter, cardiomyopathy of obscure etiology, is a disease which has yet to have a well developed clinical pattern described.

Beriberi Heart Disease

Beriberi heart disease represents a disorder of the cardiovascular system caused by malnutrition leading to thiamine deficiency. Two forms are currently recognized: the first is a well recognized reversible hyperkinetic circulatory state; the second is a neither well recognized nor proven irreversible hypokinetic circulatory state. The disorder arises as a result of a combination of factors which affect the circulatory system: (1) a defective energy production by the myocardial tissue, (2) a state of peripheral vasodilatation and arterial-venous shunting and (3) a disorder of vasomotor activity.

Pathophysiology

Thiamine is a 2, 5-dimethyl-6-amino pyrimidine united with 4-methyl-5-hydroxy-ethylthiazol and it is necessary for four reactions in intermediary metabolism. In the first, pyruvic acid is decarboxylated in the opening step of the reactions which feed into the citric acid cycle, and "active acetaldehyde" exists transiently on the thiamine before it is transferred to the oxidized form of lipoic acid. The second reaction occurs in a later step in the citric acid cycle. Here delta-ketoglutaric acid is decarboxylated and "active succinyl semi-aldehyde" exists in a transient fashion on the thiamine before it is transferred to lipoic acid. In the third reaction, in the direct oxidative pathway of glucose, thiamine is a coenzyme and carries "active glycoaldehyde". The fourth reaction involves alcohol metabolism. Alcohol is oxidized to acetaldehyde and then to acetic acid which enters the pathway of fat metabolism. However, the "active acetaldehyde" derived from the decarboxylation of pyruvate may use the acetaldehyde from alcohol oxidation to form acetyl methyl carbinol which is excreted in the urine. This latter mechanism is necessary when an alcohol load is imposed on the organism to prevent acetaldehyde from accumulating. However, the "active acetaldehyde" would not be available in the thiamine-deficient state.[6] Thiamine deficiency leads to a condition in which the intermediary metabolism of carbohydrate is severely deranged, and pyruvate, lactate, acetaldehyde and possibly other potentially toxic materials accumulate. Although the cardiac muscle is dependent upon carbohydrate metabolism for its energy, its derangement alone is not enough to cause symptoms of heart disease. There must be the added factor of increased venous return caused by peripheral vasodilatation. The mechanism of the vasodilatation is unknown; but it has been suggested that there is a disorder of vasomotor innervation,[7] and that elevated levels of blood pyruvate and lactate cause peripheral vasodilatation.[8]

Pathology

The pathologic lesions seen in beriberi heart disease are nonspecific and do not appear to be of an irreversible type. The major pathologic features are ventricular dilatation, usually with some increase in cardiac mass. Hydropic cellular changes and interstitial edema are the microscopic features. There is no cellular infiltration or fibrosis.[9]

Clinical Manifestations

The clinical manifestations of beriberi heart disease are variable. In the milder cases exertional dyspnea and edema are the complaints, and findings of a hyperkinetic circulation are noted — bounding pulses, systolic hypertension, tachycardia, systolic arterial sounds and a short circulation time. The illness may proceed to overt cardiac failure with narrow pulse pressure, orthopnea or pulmonary edema, cardiomegaly, pulmonary and systematic venous engorgement with elevated venous pressures. A very severe and agonizing form of cardiovascular failure may be seen, and this is termed Shoshin beriberi. Here there is a marked degree of restlessness, precordial discomfort, marked breathlessness, peripheral cyanosis and shock. This form is rapidly fatal. The overt clinical state is usually provoked by some undue exertion, increased environmental temperature or febrile disease, which leads to increased cardiac work and peripheral vasodilatation. It must also be considered as a potential complicating factor in heart disease of other etiology. Functional studies show accelerated peripheral circulation, elevated venous pressure, elevated right ventricular systolic and end systolic pressures, lowered total pulmonary resistance and lowered total peripheral resistance with edema and no cyanosis.[10,11,12] This description is that of the well recognized form of beriberi heart disease causing heart failure associated with increased cardiac output.

Alcoholic Heart Disease

In 1946 one investigator[13] suggested that the criteria for diagnosis of beriberi heart disease be broadened to include those in patients in whom no other cause for heart disease was found, who consumed a thiamine-deficient diet, who had signs of neuritis or pellagra, who had an enlarged heart with sinus rhythm, elevated venous pressure, dependent edema and recovery on treatment with decrease in the heart size. These criteria are not valid, however, since no evidence has shown that the condition results from a thiamine-deficient state, that thiamine alone will cure it, or that thiamine deficiency will lead to an irreversible form of cardiac failure. It is also a hindrance to stimulation for clinical investigation, since it would furnish a label for myocardial disease of otherwise obscure etiology, which may be due to other nutritional deficiencies or alcoholic myocardial toxicity.

An isolated form of myocardial failure is seen not infrequently in Fiedler's myocarditis, chronic myocarditis, myocardosis, idiopathic myocardial

Continued

hypertrophy, asymmetrical hypertrophy, fibroelastosis, myocarditis with endocardial elastomyofibrosis and endomyofibrosis.

Symptoms

The onset is in middle or late adult life and is insidious. The symptoms are palpitations, breathlessness and pain, as a result of embolic phenomena. The palpitations may be the result of paroxysmal rhythm disturbances, precipitated by alcohol ingestion. However, sinus tachycardia and atrial fibrillation of a constant nature may be seen in the later stages of the disease. Paroxysmal nocturnal dyspnea may occur; but this is not so prominent a feature of the disease as it is in coronary artery and hypertensive disease, since both ventricles fail simultaneously. Rather the breathlessness occurs at rest or on exertion, and orthopnea may be present. Biatrial and ventricular thrombi are a striking feature and give rise to pulmonary and systemic embolic phenomena. The history of alcoholism is frequently elicited. Since the usual intake of the alcoholic — two quarts of wine, a quart of whiskey or 15 bottles of beer daily — along with some supplemental carbohydrates, satisfies the caloric needs, the malnutrition is not readily evident by the bodily appearance.

Physical Findings

Physical examination usually shows a tachycardia, normal blood pressure and varying degrees of tachypnea. The venous pressure may be elevated and the circulation time prolonged. A previous embolus may have caused the obliteration of one of the peripheral pulses of the lower extremities. A pleural effusion may be noted due either to cardiac failure or pulmonary embolism. The heart is enlarged with an apical impulse that is down an interspace or two from normal and out near the axilla. A gallop sound is usually noted. Systolic and diastolic murmurs may be noted when failure is present and usually disappear or become less prominent when compensation is restored, a point which serves to differentiate these murmurs from those of organic valvular disease. The liver may be felt and may be tender. Ascites and edema may be present. The chest x-ray generally reveals striking cardiac enlargement, usually of all the chambers. The electrocardiogram often shows various rhythm disturbances, intraventricular condition defects, or low voltage QRS complexes. Nonspecific ST-T changes with low voltage, flat or inverted T waves, and prolonged QT interval may be present.

The pathological picture is that of a myocardial fibrosis either diffuse or focal, often perivascular with some evidence of organization and a mild inflammatory cell infiltrate.[14,15]

Treatment

The treatment is the same as for other forms of heart failure. Absolute alcohol abstinence is essential, as is a nutritious diet and prolonged bed rest, until the maximum period of compensation is achieved. Anticoagulation is used because of prolonged bed rest and also because of the tendency toward thrombus formation in the heart and veins of the lower extremities.[16,17,18] The course is frequently one of persistent and chronic congestive heart failure with generalized cardiac enlargement, despite apparent adequate treatment and abstinence from alcohol.

Case Reports

Case 1

A 42-year-old white male, a skilled laborer, was admitted to the hospital on 11/25/65 with a chief complaint of breathlessness on exertion of four weeks' duration.

He had been in his usual state of health until a month before, when he began to note breathlessness on exertion, which had progressed in severity so that he could not go up more than a few steps without becoming short of breath. Associated with the breathlessness was an epigastric burning pain which subsided with rest. He had had no orthopnea or paroxysmal nocturnal dyspnea; there had been no previous complaints suggestive of coronary artery disease or myocardial infarction; and he had no joint symptoms and no complaints suggestive of a neuritis.

He had scarlet fever at the age of 23; his father died at the age of 66 of "scar tissue on the heart"; his mother died at age 53 of cirrhosis of the liver and alcoholism; he had five siblings and four children in good health. He drank three cases of beer a week and had done so for 24 years.

Examination showed a sinus tachycardia with a rate of 100 to 110, blood pressure of 100/60 and a respiratory rate of 18. He was afebrile. The arm to tongue circulation time was 27 seconds and the venous pressure was 30 centimeters. No rales were heard in the chest. The apical impulse was prominent in the sixth intercostal space in the left anterior axillary line and a diastolic gallop was present.

Blood counts, urinalyses, serum electrolytes, blood sugars and erythrocyte sedimentation rates were normal. Mild azotemia was present, with a normal serum creatinine. There was no conclusive evidence of hepatic cirrhosis. A protein bound iodine was 8.3 micrograms per cent. Chest x-rays revealed generalized cardiac enlargement. The electrocardiogram showed a sinus tachycardia with flat T waves. One month after admission he had a pulmonary embolus to the right lower lobe. He responded slowly to therapy (digoxin, diuretics, salt restriction, and bed rest) with gradual decline in the pulse rate, but the heart size remained large.

Case 2

A white male, an unemployed, unskilled laborer, was admitted to the hospital on 10/22/63 with a complaint of chest pain and cough of a week's duration.

He had had a chronic cough, but it had become more severe during the previous week. The chest pain was pleuritic in nature and aggravated by the cough. He also complained of fatigue, lethargy and insomnia. He had no orthopnea or paroxysmal nocturnal dyspnea.

He had been seen here previously and had been in fair health except for his alcoholism. His mother and father and one sibling were in good health.

The blood pressure was 110/55, pulse 80 and regular, and respiratory rate 18. He was afebrile. The lungs were clear. The heart was enlarged to the left. The electrocardiogram showed a sinus rhythm and QT interval of 0.44 seconds. The chest x-ray showed a generalized cardiac enlargement. The blood count, urinalysis, VDRL and blood urea nitrogen were normal. Liver function studies were normal.

A diagnosis of beriberi heart disease was made. He was treated as an outpatient with thiamine, 100 milligrams twice daily, for a month.

He was admitted again on 1/22/64 with a lung abscess. The cardiovascular system was normal at that time.

His last admission was on 11/23/64 when he died suddenly in the emergency room after having a seizure. At autopsy the heart weighed 500 grams and was dilated. The microscopic pathology showed some fatty infiltration and some minimal cellular degeneration and fibrotic replacement. The lungs revealed pulmonary hemorrhage and congestion. The final cause of death was cardiac failure of undetermined cause accompanied by acute pulmonary edema.

It is interesting and perhaps of significance that between October 1963 and January 1964 this patient's congestive heart failure and cardiac enlargement completely cleared on thiamine alone without the use of digitalis, diuretics, or salt restriction. He persisted in his alcoholism and died one year later, again suffering from congestive heart failure and cardiac enlargement.

George Kitzmiller, M.D.
Chief Medical Resident

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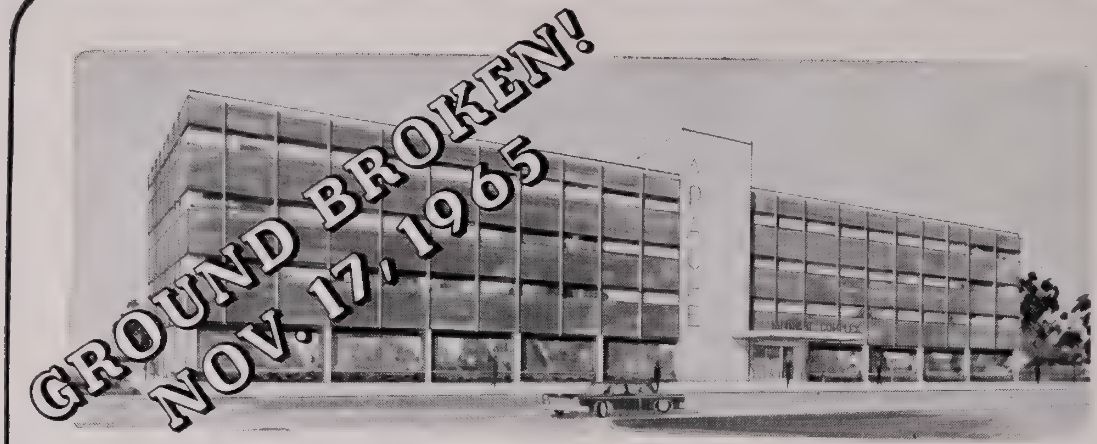
3-18 May be secured from the Grand Rounds Editor.

The man who has committed a mistake and doesn't correct it is committing another mistake. — Confucius


GROUND BROKEN!
NOV. 17, 1965

APACHE PLAZA MEDICAL COMPLEX

"Standing in the middle of a boomtown in the North . . . in the middle of a 'doctor-poor' area"—*Mayor James McNulty, St. Anthony Village, in a speech at the ground-breaking ceremony for Apache Plaza Medical Complex, November 17, 1965.*

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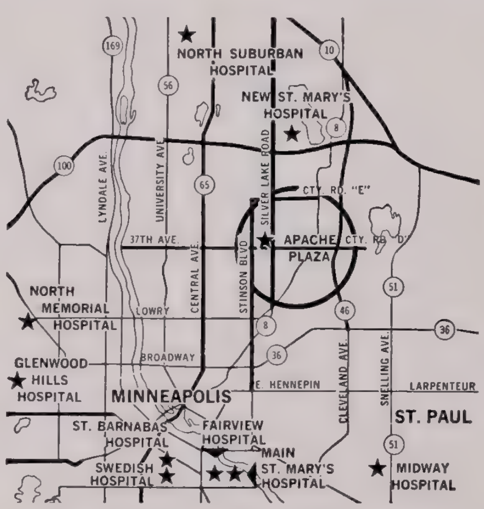
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APACHE PLAZA MEDICAL COMPLEX

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Systemic Manifestations of Cancer

WILLIAM F. NUESSLE, M.D.
Minneapolis, Minnesota

MIGRATORY THROMBOPHLEBITIS, clubbed fingers, or the flush from carcinoid may be the first clue to the physician in his continual search for malignancy. Systemic manifestations of cancer often bear no direct relationship to primary or metastatic tumor, but rather occur at a distant site through humoral or neural influences. This secondary tumor effect may precede the visible onset of the tumor, and it may disappear following removal of the neoplasm. Study of the mechanism by which malignancy produces systemic change affords the physician a helpful means to unravel unknown facets of the cancer problem, including the cause.

Metastases to the liver, brain, or other organs frequently occur in cancer, producing dramatic effects which may dominate the clinical picture. Some of the lesser known remote effects of cancer, most of which are not related to metastases, are summarized in the Table.

Nutritional

Weight loss and cachexia have long been known as signs of cancer. Waterhouse[1] reviewed malnutrition in malignancy and indicated a triad which characterizes this host response: (1) anorexia with diminished food intake; (2) hypermetabolism for the nutritional state of the individual; and (3) wasting of body tissues. She found that the wasting affects primarily muscle and fat but probably involves all organs except the liver and brain.

Carcinoid

Carcinoid with its intriguing serotonin effect has been the basis of recent extensive medical and biochemical study. As aptly put by Moertel and coauthors,[2] almost as many papers have been written about carcinoid as there are reported cases. This neoplasm, characteristically found in the small intestine where it often metastasizes to the liver, may produce episodic flushing, watery diarrhea, and cardiopulmonary symptoms, especially bronchospasm.

Credit has been given to Lubarsch for his description of this unique small bowel tumor which he termed "little carcinoma" and to Oberndorfer who coined the term carcinoid to signify this tumor's apparent benign nature.[2,3,4] Masson[5] suggested the term "argentaffin tumor" in view of its silver-staining properties. He felt that the tumor arose from the cells of Kultschitzky in the crypts of Lieberkuhn and had a probable endocrine effect.

The location of carcinoids is usually in the gastrointestinal tract, especially the appendix and ileum. Carcinoids are the most common small intestinal tumors found at necropsy, present in 28% of a reported group.[2] They also occur in the bronchi,[6] ovaries,[7] bile ducts, and pancreas.[8]

Although first thought to be benign, carcinoid is now considered a malignant tumor.[4] In a study of 207 patients with small intestinal carcinoid, Moertel[2] found 64 with me-

Continued

tastatic lesions. Fifty-six of this group of 207 had functioning tumors. Ninety-three per cent of these carcinoids producing serotonin were found to have metastasized. Carcinoids have been found to be multiple in 29% of the cases.[2,4] Patients have had 40 and 68 primary carcinoid tumors.[4]

Carcinoid is often associated with other malignant disease.[2,4] Moertel[2] found coexistent malignant disease in 29% of his group, especially in the colon, stomach, breast, and lung. Bronchial carcinoid is more often associated with acromegaly, pluriglandular adenomatosis, and Cushing's disease than are other carcinoids.[8]

The functioning carcinoid usually produces excessive quantities of the vasopressor agent, serotonin (5-hydroxytryptamine).[9] Under ordinary circumstances only one per cent of ingested tryptophan is metabolized by way of the tryptophan-serotonin pathway. In the malignant carcinoid syndrome, 60% is so used.[10] Measurement of the serotonin metabolite 5-hydroxyindoleacetic acid (5HIAA) in the urine furnishes the most reliable guide to detection of this syndrome.[10,11]

The serotonin from carcinoid produces a wide range of symptoms.[9] Vasomotor changes include the characteristic flushing, plethora or cyanosis, and telangiectasis. The primary gastrointestinal effect is persistent diarrhea, but anorexia, nausea, and weight loss also occur. Cardiopulmonary manifestations include wheezing and bronchoconstriction as well as right and, occasionally, left[8] heart lesions. Acquired pulmonary stenosis or tricuspid regurgitation occurs[9] with thickening of the valvular endocardium.[12] Central nervous system symptoms may also be present.

The flush, which may be misinterpreted as menopausal in origin, often occurs spontaneously but may also be induced by various

TABLE 1
Classification of the Systemic Signs of Cancer

A. Nutritional
    1. Cachexia
    2. Skin Lesions (see I-13)

B. Endocrine
    1. Carcinoid
    2. Hypoglycemia
    3. Cushing's Syndrome (with hyperglycemia)
    4. Adrenal Insufficiency
    5. Increased Antidiuretic Hormone
    6. Hypercalcemia
    7. Gynecomastia

C. Skeletal
    1. Clubbing
    2. Osteoarthropathy
    3. Arthralgia
    4. Gout

D. Muscle
    1. Myasthenia Gravis (see H-4)
    2. Carcinomatous Myopathy (see H-4)

E. Hemopoietic
    1. Anemia
    2. Erythrocythemia
    3. Leukemoid Reactions
    4. Cryoglobulinemia
    5. Hemorrhagic Tendency

F. Cardiorespiratory
    1. Hypertension
    2. Thrombophlebitis
    3. Endocarditis
    4. Unilateral Lymphedema

G. Alimentary
    1. Polyposis (Peutz-Jeghers, see I-11)
    2. Zollinger-Ellison Syndrome
    3. Hypokalemic Diarrhea

H. Nervous System
    1. Mental Symptoms
    2. Cortico-cerebellar Degeneration
    3. Peripheral Neuropathy
    4. Neuromuscular Disorder
    5. Meningitis

I. Skin
    1. Dermatomyositis
    2. Acanthosis Nigricans
    3. Bowen's Disease
    4. Other Skin Cancer
    5. Herpes Zoster
    6. Dermatitis Herpetiformis
    7. Pruritus
    8. Urticaria
    9. Erythema Multiforme
    10. Erythema Gyratum Repens
    11. Peutz-Jeghers Syndrome
    12. Anhydrosis
    13. Acquired Ichthyosis
    14. Acquired Hyperkeratosis

procedures including histamine injection,[13] alcohol ingestion,[4] defecation,[4] enemas,[14] operative traction of the tumor,[14] and anesthesia.[15]

Treatment is primarily surgical. As much of the tumor should be removed as possible to reduce serotonin formation.[16] Surgical resection of a large liver metastasis has afforded distinct symptomatic relief.[15,17] Temporary relief can often be obtained by restricting dietary tryptophan content. Benefit by the use of serotonin antagonists including cyproheptadine (Periactin) or methysergide maleate (Sansert) and chlorpromazine (Thorazine) has been reported.[8,15,18] Antitumor chemotherapy has produced a significant decrease in liver size in one half of the trials, although there was an initial exacerbation of carcinoid symptoms.[19]

Hypoglycemia

Hypoglycemic episodes may occur in patients with pancreatic islet beta cell neoplasms termed insulinomas. Only ten per cent are malignant but these cause the more intense reactions. Multiple pancreatic lesions are found in ten per cent of the cases.[20a]

Hypoglycemia may also be associated with extrapancreatic neoplasms. Lowbeer[21] collected 48 such cases from literature. There were 25 tumors of mesodermal origin and 23 epithelial tumors. Various sarcomas were the most common tumor. There were 16 patients with primary carcinoma of the liver and five with adrenal carcinoma. Hypoglycemia has been observed in nine of 27 Chinese patients with primary carcinoma of the liver.[22] It is postulated that hypoglycemia results from production of an insulin-like substance by the tumor,[21] and such a substance has been found in bio-assay.[23]

Cushing's Syndrome*

Cushing's syndrome is often associated with tumors of the adrenal and pituitary glands but may also be present in other sources of malignancy. Riggs and Sprague[24] reviewed the findings in 232 patients with Cushing's syndrome. Seventeen (7.3%) had clinically evident pituitary tumors. The adrenal glands were explored or examined in 203 cases. Adrenal hyperplasia was present in 151, benign cortical adenoma in 27, and cortical carcinoma in 25 (12.3%) instances.

The majority of the "other malignancies" associated with Cushing's syndrome have been oat-cell carcinomas of the lung. Other neoplasias have been reported including other forms of bronchogenic carcinoma as well as malignancy of the ovary, testis, prostate, thymus, pancreas, thyroid, colon, and sympathetic chain.[25-29] Symptoms of hyperadrenocorticism may usher in the presence of pulmonary malignancy and often precede those of the tumor by several months.[25]

Two forms of hyperadrenocorticism occur. The first is typical Cushing's syndrome with the rapid onset of weight gain and peripheral edema, moon facies, an enlarged cervical fat pad, purple striae, hypertension, and diabetes mellitus. The second form does not show all the features of Cushing's syndrome but rather progressive weakness with hypokalemia, wasting, and death.[30]

In malignant disease associated with Cushing's syndrome, the adrenal glands are often found to be enlarged on pathological examination. The adrenal cortex shows hyperplasia affecting the zona fasciculata and zona reticularis but not the zona glomerulosa. Elevation of the urine excretion of 17-hydroxycorticosteroids, 17-ketogenic steroids, and 17-ketosteroids has been demonstrated.

Liddle et al.[26,28,31] have shown that the nonendocrine tumors secrete a polypeptide which is similar to pituitary adrenocorticotrophic hormone both chemically and biologically. The corticotropin-like substance has been demonstrated in the plasma and from extracts of the primary and metastatic tumor. It is assumed that the ACTH-like substance promotes growth of the adrenal cortices and that this augments secretion of corticosteroids. High levels of corticosteroids suppress the synthesis and secretion of adrenocorticotropin by the pituitary.[31]

Adrenal Insufficiency

Addison's disease may occur from metastatic carcinoma especially of the lung, while the primary lung tumor may remain virtu-

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*See Minnesota Med 49:244, 1966.

ally asymptomatic.[32] In a large series of patients with lung cancer, 34% first sought medical attention because of symptoms which were due wholly or in part to metastatic lesions.[33] Forty per cent of this group of 1,070 autopsied patients had metastases to the adrenals.

Increased Antidiuretic Hormone

The presence of bronchogenic carcinoma may alter renal function to produce loss of sodium chloride. Winkler and Crankshaw[34] first described a case of lung malignancy associated with hypochloremia. Schwartz et al.[35] felt that the syndrome of renal sodium loss with hyponatremia occurred because of inappropriate secretion of antidiuretic hormone. Biological urine assay has shown increased secretion of antidiuretic substances.[36] Extracts of the lung tumor, which is often oat-cell carcinoma, have shown antidiuretic hormone-like activity.[37]

Hypercalcemia

Hypercalcemia is frequently associated with malignancy and may be the presenting manifestation. Warwick et al.[38] found hypercalcemia in 40 of 438 patients who presented for radiation therapy of their malignancy (an incidence of 9.1%). Myers[39] studied 430 patients having hypercalcemia associated with malignancy. Over one half had cancer of the breast, but lymphoma, lung, and renal neoplasias were also common. It is apparent that most instances of hypercalcemia in malignancy are associated with metastatic bone disease, though a surprising 14.3% of Myers' group[39] and 20% of Warwick's series[38] had no evident bone metastases.

Symptoms and signs of hypercalcemia include lethargy, coma, gastrointestinal and cardiorenal difficulties, including thirst, polyuria, and arrhythmia.[39] Warwick[38] found that the gastrointestinal symptoms of nausea, vomiting, anorexia, and constipation accounted for 75% of all manifestations.

Stone and co-workers[40] felt that hypercalcemia could result from metastatic bone destruction with release of calcium, but that tumor parathormone-like substance or tumor parathyroid-stimulating substance may also occur. They thought that tumor production of "substance X" which stimulated the parathyroid glands was most likely. Stone reversed hypercalcemia with surgical removal of parathyroid glands showing pathological findings consistent with secondary hyperplasia. Others feel that the tumor itself produces a biologically active parathormone substance. Serum bio-assay[41] and immunological assay of primary and metastatic tumor[42] have demonstrated such a substance. It would appear that all three mechanisms may play a role in the production of hypercalcemia.

Gynecomastia

Precocious sexual development including breast enlargement in a young girl is a well known sign of the rare thecal cell tumor of the ovary.[20c] Gynecomastia in a man may be a sign of underlying carcinoma of the lung,[43-46] hepatoma,[47] or choriocarcinoma of the testis.[20b] The gynecomastia may be the presenting complaint[43] and may disappear after the removal of the tumor.[43,47] At times the gynecomastia is associated with clubbing or hypertrophic pulmonary osteoarthropathy[43-46] or adrenal hypertrophy.[46] Increased urinary estrogens have been observed,[44-46] becoming normal after removal of the lung cancer.[46] However, Ginsberg and Brown[45] found no correlation between the presence of gynecomastia and the level of the urinary estrogens.

Pulmonary Osteoarthropathy

Remote skeletal symptoms may herald the onset of a serious visceral disease, often bronchogenic carcinoma. The skeletal manifestations may be divided into three categories—clubbing, osteoarthropathy, and arthralgia. Clubbed (Hippocratic) nails are thickened and curve over the ends of the digits which are widened distally. Osteoarthropathy (Bamberger-Marie disease) refers to periosteal thickening especially of the distal long bones. Arthralgia may be simple joint pain related to osteoarthropathy or a full-blown rheumatoid arthritis. Arthralgia often brings the patient to the doctor; clubbing is an obvious physical finding; while osteoarthropathy may be noted on physical inspection but is verified by radiographic examination.

Clubbing of the fingers is probably an early stage of secondary hypertrophic osteoarthropathy.[48] Hansen[49] believes that clubbing is more apt to occur in diffuse lung disease such as bronchiectasis. He feels that osteoarthropathy is often found in localized pulmonary lesions including cancer or abscess, with the skeletal manifestations developing and disappearing more rapidly. Clubbing, periostitis, and synovitis have been considered a classical triad in pulmonary osteoarthropathy.[50]

Hypertrophic osteoarthropathy may be an idiopathic familial disorder termed pachydermoperiostosis. This syndrome is characterized by clubbed nails, bony changes, coarse facial features, and thickened skin producing a furrowed forehead and bulldog scalp.[51,52] This idiopathic or primary osteoarthropathy cannot be distinguished from the form secondary to pulmonary disease. The presence or absence of a primary lesion and the clinical course are necessary to differentiate the two forms.[52]

Although tuberculosis has been considered an important etiological factor in the past,[48] recent reports suggest that this disease rarely produces hypertrophic osteoarthropathy.[50,53] Carcinoma of the lung is felt to be the chief cause of osteoarthropathy.[49,53-58] Hammarsten and O'Leary[53] reviewed 25 papers in the English literature and found that of 91 cases of hypertrophic osteoarthropathy, 79 were associated with pulmonary neoplasm. Wierman et al.[55] noted articular manifestations in 5.2% of 481 malignant lung lesions treated surgically. Alvarez[54] carried out resection in 47 patients with carcinoma of the lung. In 12 of the 47 the earliest manifestation of the disease was "the rheumatoid syndrome of the type of Bamberger-Marie." An unusually high incidence of osteoarthropathy is present in mesothelioma. Claggett[59] found that 16 of 24 cases of localized fibrous mesothelioma of the pleura showed articular manifestations, the latter often bringing the patient to the physician.

Studies in Germany have shown increased vascularity in clubbed fingers as evidenced by enormously dilated vessels in the nail beds using capillaroscopic technique.[50] Postmortem arteriograms of clubbed fingers using barium sulfate suspension showed that arteries and arterioles were more numerous. Their lumens were widened and the ungual processes were covered with an unusually heavy arteriolar network.[60] The increased vascularity was felt to produce an increase in the tissues of the tips of the digits especially the fibrous elastic tissue of the nail beds. Unilateral clubbing has been reported in arteriovenous fistulae producing increased blood flow in the affected extremity, with regression of the clubbing following surgical correction of the fistula.[61] Surgical removal of the related bronchogenic carcinoma often produces dramatic relief of the articular symptoms.[49,53,55,56,58] Radiographic examination several months after surgical removal of lung tumor has shown absorption of subperiosteal new bone and disappearance of osteoporosis in the long bones affected by osteoarthropathy.[56] Rheumatoid arthritis associated with carcinoma of the prostate has been symptomatically cured with estrogen therapy,[62] and that related to breast carcinoma has been alleviated with testosterone.[63]

Flavell[57] believes that only a neural reflex could explain the abrupt and consistent cessation of the pain of osteoarthropathy which follows resection of lung tumor. He performed vagotomy on five patients with inoperable bronchogenic carcinoma and hypertrophic osteoarthropathy. The neural surgery produced dramatic relief of articular pain and disappearance of joint swelling.

Gout

Gouty arthritis occasionally occurs in leukemia and other malignancy. In a series of 520 patients with gout, Kuzell et al. found that six were secondary to leukemia, Hodgkin's disease, and multiple myeloma.[64] Lynch[65] found hyperuricemia in 72 of 116 patients with leukemia, with three instances of gouty arthritis. The hyperuricemia is felt to result from increased catabolism of nucleic acid of the leukemic cells.[66]

Anemia

In an excellent analysis by Hyman[67] the

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problem of anemia in malignancy was recently reviewed. Since the pathologic studies of Virchow in the late 19th century, anemia in cancer patients has been thought by many to be related to bone-marrow replacement by tumor cells. Newer studies have shown that multiple factors play a role. Blood loss from a bleeding tumor frequently produces anemia and may bring the patient to the doctor. Hemolytic factors are often important in malignancy, especially lymphoma.

Erythrocythemia

Ruddy facies, a laboratory report of elevated hemoglobin, or other signs of polycythemia may be associated with, and possibly the first sign of, renal or hepatic malignancy. Erythrocythemia is felt to be a better term than polycythemia, for in cancer, erythrocytosis is present without splenomegaly, leukocytosis, or thrombocytosis.[68-70]

In Hypernephroma

In 1958 Damon and co-workers[68] presented ten patients with erythrocytosis and renal carcinoma and reviewed 12 other reports from the literature. The ten cases represented 4.4% of 205 patients with polycythemia and 2.6% of 350 individuals with renal carcinoma. Thiel in Germany found polycythemia in 5.6% of renal malignancy at autopsy.[71] The erythrocythemia is often corrected by surgical removal of the diseased kidney.[68,69,71] Erythropoietin, usually found in the normal kidney, has been found to be increased in the plasma in these patients[71] and is felt to be the bone-marrow stimulus to red cell production.[68,71] If hematuria occurs in a patient with polycythemia, urologic investigation is essential.[68]

In Hepatoma

Working with Chinese patients in Hong Kong, McFadzean and associates[70,72] demonstrated a high incidence of erythrocythemia in 145 patients with hepatocellular carcinoma. They found 17 patients (11.7%) in this category.[70] Plasma erythropoietic stimulating factor was not increased in four patients studied. Only scattered American cases have been reported.[73-75]

Leukemoid Reactions

The finding of a leukemoid reaction in the laboratory should alert the physician to the possibility of cancer. The increase in granulocytes, especially eosinophils, usually means metastatic carcinoma and thus a poor prognosis.[69,76] Leuko-erythroblastosis refers to an increase in the circulating blood of immature leukocytes of the myeloid series and also nucleated red blood cells which may occur in cancer of the breast, prostate, lung, and other organs.[77a]

Cryoglobulins

Laboratory detection of cold-precipitable serum proteins (cryoglobulins) may be the initial finding in cryptic cancer. Cryoglobulinemia occurs most often in multiple myeloma or macroglobulinemia but may also be present in chronic lymphatic leukemia, lymphosarcoma, and other malignancy.[77b,78]

Cryofibrinogenemia has been detected in patients with neoplastic and other disease. Its presence may account for the clinical paradox of intravascular clotting appearing simultaneously with hemorrhagic diathesis.[79,80]

Hemorrhage

Hemorrhage as a sign of malignancy may occur from thrombocytopenia in leukemia, lymphoma, and other malignancy.[81] Fibrinolytic purpura occurs in prostatic and other cancer, possibly from fibrin destruction by the enzyme, fibrinolysin.[82] Hypofibrinogenemia has been a problem in patients with carcinoma of the pancreas and stomach.[81]

Hypertension

Hypertension may be an indication of excessive catecholamine hormone secretion from a pheochromocytoma. Epinephrine produces paroxysmal* and norepinephrine sustained hypertension. Approximately ten per cent of these tumors are malignant.[83]

Thrombophlebitis

Thrombophlebitis migrans or deep vein thrombosis is often seen in association with cancer, especially of the pancreas, but also of the lung, stomach, gallbladder, uterus, and ovary,[84-88,89b] and may occur as a complication of extensive malignancy. Often, however, the venous disturbance may occur before other specific signs of malignant disease and may be the harbinger of the presence of occult cancer.

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*See Test Your Word Score Page 607.

Historical

Trousseau[90] first described a relationship between thrombophlebitis and cancer. Barker[91] found that in noninfectious systemic disease complicated by venous thrombosis and embolism, 27 of a group of 58 had malignancy. In 1938 Sproul[8 4]studied the frequency of carcinoma and thrombosis in 4,258 necropsies at Presbyterian Hospital in New York and found that in carcinoma of the body or tail of the pancreas 56.2% showed distant venous thrombosis. Thromboses were multiple in 31.3% of this group. In carcinoma of the head of the pancreas, 16.1% had thrombosis with 9.7% multiple. Of five with carcinoma of the body or tail of the pancreas who also had multiple thromboses, four showed nonbacterial vegetations on the mitral or aortic heart valves. Perlow and Daniels[86] reported ten instances of venous thrombosis in malignancy. Six of the ten cancers occurred in the pancreas and the lung. Seven of this group of ten were inoperable when the thrombosis occurred. In 1956 Wooling and Shick[87] described 15 cases of unsuspected malignant disease in which thrombophlebitis was the principal symptom which lead the patient to the doctor. Three originated in the pancreas and three in the ovary. Wright et al.[92,93] reviewed the records of 1,400 patients with the diagnosis of venous thrombosis or thrombophlebitis. Eighty-one of these had associated cancer, with 19 originating in the lung and ten in the pancreas.

Etiology

In patients with cancer, predisposing factors such as injury, surgery, pregnancy, blood dyscrasia, and varicosities may play a role in the production of thrombophlebitis.[86,87] However, it would appear that a humoral influence producing hypercoagulability often precipitates thrombosis in malignancy.[84,92,93]

Tissue destruction with release of tissue thromboplastin which would predispose to thrombosis has been considered. However, thrombophlebitis often antedates the symptoms of tumor when tissue destruction would be minimal.[94]

Sproul found that the nonbacterial valvular vegetations occurring with thrombosis in malignancy were composed of masses of fibrin and represented evidence of a hypercoagulability state.[84] Evidence of hypercoagulability was found by Amundson and coworkers[95] in 22 of 30 patients with various malignant diseases. There were elevated levels of antihemophilic globulin as measured by an accelerated thromboplastin generation test.

Manifestations

Durham indicated in 1955 that two types of thromboses occur in visceral carcinoma.[85] The first is indistinguishable from ordinary thrombophlebitis while the second is thrombophlebitis migrans. Bilateral phlegmasia cerulea dolens (massive venous thrombosis) with terminal gangrene of the feet,[86] and renal vein thrombosis producing a nephrotic syndrome[96] have been reported. Some feel that metastatic lesions usually have occurred by the time thrombosis first develops.[89b]

Persistence of an elevated sedimentation rate in a patient with thrombophlebitis should make one consider malignancy.[87] If a patient has had two or more episodes of idiopathic thrombophlebitis, a diligent search for underlying neoplasm should be made.[85-87,97] If a person with migrating thrombophlebitis shows embolic phenomena from apparent nonbacterial endocarditis, a diagnosis of visceral carcinoma can be made almost without question.[85]

Thrombophlebitis related to malignancy responds poorly to anticoagulant therapy with frequent recurrent phlebitis and pulmonary emboli.[86,87] Thrombophlebitis which is resistant to anticoagulants is often the first indication of malignant disease.[92,93] Recurrent thrombophlebitis may cease with removal of an associated malignant tumor.[87,89b,93,97]

Unilateral Lymphedema

Unilateral lymphedema of an extremity may be the initial complaint or the only finding in a patient with neoplastic disease.[98]

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The malignancy may be a lymphoma or may originate in the prostate, testes, uterus, vulva, or breast.[89a,98] Lymphangiography has been advocated to differentiate primary and secondary lymphedema.[98]

Zollinger-Ellison Syndrome

Intractable peptic ulcer with production of copious amounts of gastric acid may be a sign of underlying malignant disease. In 1955 Zollinger and Ellison described this syndrome with tumor of the pancreatic islets which they felt produced a humoral factor inducing gastric hypersecretion and peptic ulcer.[99] Pancreatic tumor has been found to be malignant in one half of the cases,[100] with benign hyperplasia or adenoma in the others.

Priest and Alexander in 1957[101] called attention to the associated diarrhea which is often profound, inducing electrolytic loss and life-threatening hypokalemia.[101-103] Diarrhea has been found in 25% of patients with the Zollinger-Ellison syndrome[104] and is the only symptom in ten per cent of the cases.[105]

Pathology

Of the pancreatic tumors that are malignant one third are metastatic when first discovered.[106] The secondary tumor tissue usually found in the liver or surrounding lymph nodes often continues to function after the primary tumor is removed, so that the ulcer diathesis remains a problem. Of the benign ulcerogenic pancreatic growths 20% are aberrant,[100] while 12% are found to be simple hyperplasia.[104] The pancreatic nodules representing carcinoma or adenoma, which vary in size from 2 millimeters to 6.5 centimeters, are multiple in 10 per cent of the cases.[104]

Histopathology

Bloodworth and Elliot[107] studied pancreatic islet-cell lesions including hyperplasia, neoformation, adenoma, and carcinoma. They found the four islet-cell types: namely, alpha, beta, delta, and "non-specific" cells. Secretory granules were found in the alpha and beta cells. Proliferation of the alpha cells was found in pancreatic neoplasia associated with the ulcerogenic syndrome.

Gastrin

Gastrin is an endocrine hormone found in the gastric antrum which passes to the parietal cells of the stomach by diffusion or the blood stream to induce gastric secretion.[108] In 1960[109,110] a gastrin-like secretagogue was extracted from pancreatic islet-cell tumors in patients with the Zollinger-Ellison syndrome. The gastrin-like substance has been extracted from metastatic nonbeta islet-cell tumor[105,111] but has also been found in beta-cell insulinomas[111] and to a lesser extent in normal pancreas.[112]

Pathophysiology

It is assumed that the alpha secretory cells in the pancreatic neoplasia of patients with Zollinger-Ellison syndrome produce excess amounts of gastrin which cause gastric hypersecretion and hyperacidity. In 31 cases where 12-hour gastric aspiration was measured the volumes of gastric juice ranged from 350 milliliters to 6,900 milliliters, with an average of 2,500 milliliters.[104] The diarrhea is felt to be a direct result of gastric hypersecretion.[106] Steatorrhea and other signs of malabsorption have been reported,[113] possibly from inactivation of lipase and other pancreatic enzymes by the overwhelming acidity in the upper intestine. In a review of 86 documented cases, Christlieb and Schuster[104] found that the initial symptoms were epigastric pain in 81%, vomiting in 51%, weight loss in 36%, and diarrhea in 25%. Gastrointestinal bleeding in the form of melena (21%) and hematemesis (15%) was common. The pancreatic malignancies are slow-growing and the symptoms of peptic ulceration remain the predominant problem.[114]

Therapy

Medical management has been noncurative in the Zollinger-Ellison syndrome. Gastric resection with surgical removal of pancreatic tumors is the treatment of choice.[102,104,105,114,115] Surprisingly, a 20-month remission of peptic ulceration and diarrhea has been reported following single lymph node biopsy.[116]

See Minnesota Med 46:864, 1963.

Pluriglandular Syndrome

Hyperplasia and adenoma of other endocrine glands occur frequently in the Zollinger-Ellison syndrome.[106,114] There appears to be a relationship to multiple endocrine adenomatosis described by Underdahl et al.[117] in 1953. They reported two or three adenomas of the pituitary gland, pancreatic islets, and parathyroid gland which occurred simultaneously in eight patients, with review of 14 other cases from the literature. In 1954, Wermer[118] reported adenomatosis of the same glands in a man and four of nine siblings. He felt that this apparently inherited syndrome was caused by a dominant autosomal gene with a high degree of penetrance. Wermer called attention to the greater frequency of peptic ulcer in patients with endocrine adenomatosis.

The relationship of the inherited adenomatosis to the Zollinger-Ellison syndrome is uncertain. Pender[119] described a man with typical ulcerogenic tumor, whose daughter had had an islet-cell insulinoma removed.

Roth and Vilardell[120] studied patients with pituitary adenomas and found peptic ulcer to be common where there was polyglandular endocrine adenomatosis. In those with the latter syndrome, peptic ulcer was present in 16 of 28 patients with pancreatic adenoma and in 13 of 31 patients with parathyroid adenoma.

In the review of the Zollinger-Ellison syndrome by Christlieb and Schuster, tumors of other endocrine glands were found in 37% of cases and in 50% of those autopsied.[104] Neoplasia of the parathyroid, adrenal, and pituitary glands was common, but that of the thyroid and beta-cell pancreatic islets was rare. Carcinoid is also implicated in this syndrome. Williams and Celestin[121] reported an interesting case of bronchial carcinoid in a patient who also had multiple adenomas of the pituitary, parathyroid, pancreatic islets, and adrenal. Two of the pancreatic tumors were malignant, and there were metastases to nodes and liver.

Pheochromocytoma has been reported with pituitary adenoma. Increased growth hormone was suspected as a stimulus to the adrenal medulla.[122]

Cushman[123] reviewed familial pheochromocytoma and added two kindreds to ten others from the literature. There were 32 cases of pheochromocytoma in these 12 families. He felt that inheritance was by simple autosomal dominance. In one family, three individuals had two pheochromocytomas, two thyroid carcinomas, and one parathyroid adenoma. Cushman suggested that thyroid and adrenal medullary tumors might be added to the pluriglandular group.

It is likely that the alpha-cell pancreatic islet tumors are but one category in multiple endocrine glandular adenomas and carcinomas.

Hypokalemic Diarrhea

Villous adenocarcinoma of the colon may produce marked diarrhea with hypokalemia. Shamblin et al.[124] reviewed 21 cases of villous adenoma, of which eight (38%) were malignant and two (9.5%) had metastasized. Predominant symptoms were diarrhea, weakness, fainting, and shock.

Nervous System

The nervous system is a frequent site of systemic effect of malignancy. Symptoms of anxiety or depression out of proportion to physical complaints often occur in patients with carcinoma of the pancreas.[94,125,126] Mental changes varying from slight mental dullness to toxic psychosis may dominate the picture of lung cancer.[94] Various types of carcinoma have been associated with dementia, producing progressive intellectual impairment and memory failure.[127]

Historical

There have been scattered reports of neurological disorders in patients with cancer including carcinoma of the lung,[128,129] myeloma,[130-132] and lymphoma.[133] Brain and Henson[127] summarized their experience with 42 patients having neurological disease with malignancies, thirty-two of which occurred in the lung. They used the term "carcinomatous neuromyopathy" to describe the whole group. They considered the sensory neuropathies with posterior root ganglion degeneration and the cortical cerebellar degenerations with loss of Purkinje cells to be

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the purer forms.

Etiology

The cause of the neurological syndromes seen in malignancy is unknown. Considerations have included carcinotoxins, infection, sensitization, metabolic or endocrine disorders,[127] and protein derangement.[133] Brain and Henson indicate that any explanatory theory must take cognizance of the following: (1) Only a very small proportion of patients suffering from carcinoma develop neuromyopathy (about five per cent of patients with lung carcinoma); (2) There is no relation between the size of the growth and the liability to neuromyopathy; (3) The incidence of neuromyopathy is much higher in lung cancer than in carcinoma elsewhere.

Manifestations

Cortical cerebellar degeneration produces vertigo, ataxia, dysarthria, nystagmus, and dementia.

Peripheral neuropathy may produce numbness, paresthesias, ataxia, or muscular weakness. Siemsen and Meister described a patient who presented with severe orthostatic hypotension felt to be related to neuropathy from carcinoma of the lung.[134] Guillain-Barre syndrome has been reported in patients with Hodgkin's disease and lung cancer.[135]

Neuromuscular signs include weakness of limbs and trunk, diplopia, ptosis, and bulbar paresis.[127] Myasthenia has been an occasional feature[127,129] with inconstant and, at times, temporary favorable response to neostigmine. Differential diagnosis included thyrotoxic myopathy, myasthenia gravis, dermatomyositis, and polymyositis.

Laboratory

Spinal fluid protein may be elevated with neuropathy.[127,128] A majority of the cases of corticocerebellar and encephalomyelitic syndromes showed some findings on spinal tap, including lymphocytic pleocytosis, increased protein, and paretic colloidal gold curve.[127]

Treatment

Therapy for the more serious neurological syndromes is symptomatic. Only one of Brain and Henson's group improved after surgical removal of the cancer.

Richardson[136] described an unusual demyelinating disorder of the cerebral white matter, which he termed progressive multifocal leukoencephalopathy. Seventeen of 22 cases were associated with lymphoma, leukemia, and carcinomatosis. There were signs of asymmetrical disease of the cerebral hemispheres with hemiparesis present in 17, aphasia in seven, and homonymous hemianopsia in five. An auto-immune process secondary to tumor has been suggested to produce this syndrome.[137]

Cryptococcosis is a fungus infection which often produces meningoencephalitis and is prone to occur in patients with lymphoma. In 60 well-documented cases of cryptococcosis,[138] 46 had central nervous system involvement and 18 had associated malignant disease of the reticuloendothelial system.

Meningitis can occur from carcinomatosis of the meninges, and the syndrome is often characterized by lack of fever and low glucose level in the cerebrospinal fluid.[139]

Dermatomyositis

The presence of dermatomyositis necessitates an intense search for malignancy. Curtis et al.[140] found eight malignancies in 45 patients with dermatomyositis. Williams[141] reviewed 590 cases of dermatomyositis from the literature and found 92 instances of accompanying malignancy (an incidence of 15.3%). Malignancies were especially common in the stomach, female genital organs, lungs, and reticuloendothelial system. In the Curtis series,[140] the onset of dermatomyositis preceded the appearance of tumor by an average of one and a half years. Dermatomyositis frequently improves following treatment of the associated neoplasm.[140,142]

Acanthosis Nigricans

Finding the hyperpigmented skin lesions of acanthosis nigricans in adults past 40 should initiate a search for occult malignancy. Juvenile acanthosis nigricans is not related to cancer. The pigmentation which involves the basal layers of epidermis is present in confluent verrucous lesions of the axillae, nipples, umbilicus, and genital area. Related malignancy, especially in the stomach, liver, pancreas, and lung,[143,144] is present in almost 100% of the cases.[145]

Bowen's Disease

Bowen's disease is a term applied to multiple superficial basal-cell epitheliomata, often the "forerunner" of internal malignancy.[146] Peterka and co-workers[147] found cancer in 11 of 33 patients with Bowen's disease occurring in a covered area. They also found that when Bowen's disease was present in an exposed area of the body, only one in 20 had internal cancer. Graham and Helwig[148] reviewed the relationship of Bowen's disease to systemic cancer. Of 155 cases of the disease, 75 were associated with premalignant or malignant lesions. Thirty-seven of these, or 23.9%, had primary internal cancer. Haserick[144] felt that Bowen's disease was often the result of previous arsenic ingestion and also believed that the internal malignancy could be the result of arsenic intoxication.

Carcinoma of the Skin

The presence of a skin cancer increases the probability of internal malignancy. Carpenter and co-workers evaluated statistics from a large tumor clinic registry and found 2,433 patients with skin cancer. Of these, 197, or eight per cent, were found to have another malignancy. The diagnosis of basal or squamous carcinoma necessitates further search for hidden cancer.[149]

Herpes Zoster

Herpes zoster occurs commonly in malignancy, especially lymphoma. However, evidence of the neoplastic disease has been found to antedate herpes zoster in all cases.[145] Burgoon et al.[150] found only one instance of lymphoblastoma in a series of 206 patients with herpes zoster. A greater incidence occurred at the Mayo Clinic[151] where lymphoma was present in 39 of 916 patients with herpes zoster (4.2%).

In a study of patients with blood dyscrasia, Shanbrom et al.[152] found that there were no instances of herpes zoster in 81 cases of acute leukemia. However, in 303 patients with chronic leukemia, lymphoma, or myeloma, herpes zoster developed in 24, a frequency of 7.9%. They found that treatment with radiation, alkylating agents, and corticosteroids preceded the onset of herpes in 20 of these cases.

Malignant neoplasia of the hematopoietic tissues increases the likelihood of disseminated herpes zoster. In 17 cases of disseminated herpes, such neoplasm was seen in ten (59%).[153]

Dermatitis Herpetiformis

Dermatitis herpetiformis may usher in the presence of cancer of the female organs, thyroid, or stomach. Necrotic tumors are felt to be more apt to produce the skin change. The eruption may regress during treatment of the tumor and return with recurrent malignancy.[145]

Pruritus

Generalized itching is often present in lymphoma and other malignancy.[145,154] Haserick[144] feels that pruritus does not occur in cancer except when the pancreas or liver are involved. It may precede other manifestations of cancer and is therefore a valuable premonitory sign. Pruritus will often disappear when the tumor is removed and may return with recurrent malignancy.[145]

Urticaria

Persistent generalized urticaria has been found in patients with cancer of the rectum, hydatidiform mole, and Hodgkin's disease. Toxins from the tumor are felt to act as endogenous allergens. Disappearance of the cutaneous eruption follows removal of the tumor.[145]

Erythema Multiforme

Erythema multiforme may appear one to 21 days following radiation of cancer or lymphosarcoma. It is assumed that the eruption is secondary to toxic proteins absorbed following tissue destruction. Repeated radiation may cause recurrent skin disease. Erythema multiforme may also occur without radiation at the time of discovery of an associated malignancy.[145]

Erythema Gyratum Repens

Erythema gyratum repens is a rare pru-

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ritic erythematous disorder which has been described in cancer of the breast[155,156] and lung.[154] The unusual gyrate or serpiginous bands give the appearance of wooden paneling, and its borders advance slowly day by day with clearing behind. The eruption, apparently toxic, has been observed to disappear after radical mastectomy for breast carcinoma.[155,156]

Peutz-Jeghers Syndrome

Multiple polyposis of the colon which is often familial is known to be a forerunner of malignancy.[157] The Peutz-Jeghers syndrome is a rare medical curiosity with scattered mucocutaneous melanin pigmentation and gastrointestinal polyposis. Credit is given to Peutz by Jeghers[158] in his description of ten cases of this syndrome. Others were added, so that in 1957 Bartholomew's group[159] collected 75 cases including seven of their own. The Peutz-Jeghers syndrome is familial and considered a dominant inherited gene by most observers.[159-161] Approximately 40% of the patients have relatives who have both the pigmentation and polyps.[159]

Pigmentation about the mouth in an individual having abdominal pain or gastrointestinal bleeding should alert the physician to this disorder. The melanin deposits are seen on the skin of the digits, about the eyes or across the bridge of the nose, or on the mucous membranes of the lips, buccal mucosa, gingiva, or hard palate. Polypi occur in the stomach, small intestine, and colon. There is controversy whether the polypi can become malignant[162] or are simply developmental hamartomas.[159] Achord and Proctor[163] agreed that the reported 20% malignant change was debatable, but described a case with a gastric polyp and hepatic metastasis. The Peutz-Jeghers syndrome has been described in association with granulosa-theca-cell tumor of the ovary, productive of premature precocity.[164]

Anhydrosis

Anhydrosis has been shown to be the herald sign of multiple myeloma[165] and Hodgkin's disease.[166] Degeneration of the secretory cells of the sweat glands has been shown on pathological examination.

Acquired Ichthyosis

Acquired ichthyosis has been found in Hodgkin's disease, lymphosarcoma, and carcinomatosis.[145,154,166,167] Dry and cracking skin, hyperkeratotic palms and soles, and alopecia have been described. The skin has returned to normal after treatment of the cancer with x-ray and nitrogen mustard.[167] Liver damage and impairment of vitamin A metabolism are felt to induce the skin change.[145]

Hyperkeratosis

Hyperkeratosis with skin pigmentation has been found in patients with carcinoma of the lung, prostate, and breast. Application and removal of adhesive tape producing local depigmentation was recently devised as a test in these individuals.[168]

Acquired Hypertrichosis

Acquired hypertrichosis with fine lanugo hair growing on the face has been described in malignancy.[144]

Conclusions

The "mediator" of the systemic change is frequently a hormone. The pluriglandular syndrome bears an important relationship to the endocrine effect in cancer. More study is necessary to further clarify the reason why 29% of carcinoids are associated with other malignancy. Awareness of the systemic manifestations of cancer will help the clinician in earlier detection of malignancy and may give helpful information as to cause of cancer.

Random Cases of Cancer Illustrating Systemic Effect

Case 1 — Secondary Gout

The patient was a 77-year-old man who was found to have chronic lymphatic leukemia in 1960. He was treated with nitrogen mustard (mechlorethamine hydrochloride) and chlorambucil (Leukeran). General arthralgia became a problem in April of 1962. Uric acid was 7.7 mgm. %. Symptomatic relief occurred with phenylbutazone (Butazolidin). The patient was maintained on probenecid (Benemid) until his death in 1964 with little arthritic pain.

Comment: Secondary gout occurs in leukemia and other diseases of the hematopoietic system.

Case 2 — Eosinophilia

Fatigue and lassitude brought this 92-year-old male to the office in April, 1965. He gave a history of chronic bronchitis, transurethral resection of the prostate in 1949, and negative biopsy of the prostate in 1962 for a suspicious-feeling gland. Examination showed a firm prostate, moderately enlarged. The hemoglobin was 11.1 grams and the white blood count 11,350 with 41% eosinophils. Chest x-ray showed diffuse osteoblastic metastases.

The patient was referred to a charity cancer hospital where alkaline phosphatase was 180 King-Armstrong units and acid phosphatase 18 with prostatic fraction of nine units. Bone marrow showed metastatic tumor presumed to originate in the prostate. He was treated with estrogens.

Comment: Marked eosinophilia was present in this man with metastatic bone malignancy.

Case 3 — Cryoglobulinemia

This 66-year-old woman was seen during hospitalization in June, 1962. She had been bothered with a purpuric eruption and edema of her legs for two months prior to admission. There had been some indigestion. Past health had been excellent. She had had a basal-cell carcinoma removed from the left cheek in 1957. Physical examination was negative except for purpura.

In doing routine laboratory tests the laboratory technician noted a precipitate in serum left overnight in the refrigerator. Hemoglobin was 9.7 grams, white blood count 3,800, sedimentation rate 53, serum albumin 3.0 grams, and globulin 1.7 grams. Repeated tests for cryoglobulins were positive. Electrophoresis before and after cold precipitation showed that five percent of the serum proteins were cryoglobulins. An upper GI series on 7-21-62 showed an antral tumor. Gastric resection was done on 7-28-62 for lymphosarcoma of the stomach with extension to the regional lymph nodes. Surgery was followed with radiation therapy. She did well thereafter except for moderate anemia with the finding of minimal hypoplasia of the bone marrow on September 17, 1964.

Comment: Evidence of cryoglobulinemia was noted by an alert laboratory technician and subsequent studies showed lymphosarcoma of the stomach.

Case 4 — Multiple Arterial Thrombi

This 51-year-old male was admitted to the hospital October 5, 1962, because of claudication involving the left leg. Apical pulmonary infiltrate had been observed since 1943 with positive Mantoux but negative tubercular cultures. The patient smoked 40 to 60 cigarettes daily. Examination showed palpable peripheral pulses with purple mottling over the left foot. The chest x-ray showed calcified and fibroid apical infiltrate consistent with old tuberculosis with slight enlargement of the left hilus. Hemoptysis occurred. Sputum was negative for the tubercle bacillus and tumor cells. On the fourth hospital day, right hemiplegia with aphasia developed. There was progressive edema and gangrene of the left leg. The patient expired on October 31, 1962.

Autopsy showed adenocarcinoma of the left lung with metastases to the reginal lymph nodes, pleura, and liver. Old tuberculosis was present. Thrombosis of the aorta and left middle cerebral artery was evident, with left femoral and renal artery emboli.

Comment: Multiple arterial thrombi with its complications dominated the picture in this patient with lung carcinoma.

Case 5 — Widespread Thrombosis

The patient was a 79-year-old male who was admitted to the hospital on November 1, 1962, because of leg pain and edema, a sore on his right ankle which failed to heal in three months, and absent foot pulses. There was alcoholism in the past with abstinence in the previous six years. A basal-cell carcinoma was removed from his left hand in June of 1962. Gangrene of the legs developed, so that bilateral supracondylar femoral amputation was performed. Bloody diarrhea occurred, with proctoscopic examination showing beefy-red denuded mucosa. It was felt that mesenteric artery thrombosis had occurred, producing a gangrenous bowel. The patient expired November 18, 1962.

Autopsy showed general arteriosclerosis with aortic thrombosis from just below the renal arteries to the common iliac. The inferior mesenteric artery was almost completely occluded. Unsuspected carcinoma of the kidney measuring two centimeters in diameter and adenocarcinoma of the prostate were present.

Comment: Autopsy showed two malignancies not suspected before death. A basal-cell carcinoma was removed at the time of onset of symptoms. Widespread thrombosis occurred in arteriosclerotic vessels necessitating bilateral leg amputation. The basal-cell carcinoma and thrombotic tendency are likely to have a relationship with the underlying malignancy.

Case 6 — Recurrent Thrombophlebitis and Bleeding

This 61-year-old housewife was seen in consultation on April 12, 1963, because of abdominal pain and anemia of 9.5 grams. Thrombophlebitis had occurred in the right leg in December, 1962, and in the left leg in March, 1963. Examination showed a systolic heart murmur, multiple ecchymotic areas, and minimal edema of the left calf from the recent thrombophlebitis.

Gastrointestinal x-rays were negative. Platelet count was 129,000, prothrombin time 15.8 seconds, Lee-White clotting time seven minutes, and Ivy bleeding time over 20 minutes. Clot retraction was complete in two hours. Fibrinolysin test for euglobulin was negative with no lysis of the fibrin clot in two hours. Qualitative fibrinogen test was normal with beginning clot formation in nine seconds and a solid clot in 60 seconds. Prothrombin consumption

Continued

test was abnormal with a value of 16.5 and a control 31.3 seconds. Partial thromboplastin test was normal with 97.8 for patient and 70.5 for control. The tests suggested qualitative platelet deficiency. Carcinoma of the pancreas was suggested. After preparation with fresh blood, exploration was carried out on May 3, 1963, and showed a pancreatic mass and metastatic adenocarcinoma to the liver. Her condition deteriorated progressively. Gangrene of the feet occurred prior to death on June 2, 1963.

Comment: Recurrent thrombophlebitis and a hemorrhagic tendency were signs of underlying pancreatic malignancy.

Case 7 — Neuromyopathy

This 55-year-old housewife was referred for medical care on December 18, 1962, by a thoracic surgeon because of inoperable adenocarcinoma of the lung with pleural and diaphragmatic metastases. She was treated with N, N′, N″,-triethylenethiophosphoramide (Thio-Tepa) intravenously with questionable success. During this time her attitude was one of indifference. On October 14, 1963, she was admitted to the hospital after having emesis, collapse, and temporary loss of consciousness, with marked weakness of the trunk and legs. Paranoid trends and periodic mental confusion were present. Peripheral muscular atrophy and fasciculations developed. Spinal fluid showed no cells and protein of 28 mgm.%. An electroencephalogram was highly abnormal. electromyography showed no myasthenic features but needle findings and nerve conduction abnormalities consistent with polyneuropathy. Prostigmin (neostigmine) was used without benefit.

As there was increasing weakness and lack of awareness, she had difficulty holding her head up as she sat by the bedside. On February 7, 1964, she was transferred to a nursing home where she expired March 3, 1964. There was no autopsy.

Comment: The patient had a severe mixed form of carcinomatous neuromyopathy.

Case 8 — Progressive Myasthenia

In October, 1958, this 52-year-old office worker had surgical removal of the soft palate and adjacent mandible for carcinoma. Cervical lymph nodes were removed and showed metastases. She did well until April, 1959, at which time she developed nausea, blurred vision, diplopia, ptosis, and ataxia. Subjective improvement occurred with edrophonium chloride (Tensilon) intravenously. Opinion was carcinomatous myopathy of the myasthenic type. Ambenonium chloride (Mytelase) and neostigmine (Prostigmin) gave temporary relief. Increased weakness, lethargy, and coma ensued. Large doses of ambenonium chloride produced no benefit and the patient expired October 29, 1959.

Autopsy showed no evidence of metastatic tumor. The cerebrum and cerebellum showed minimal diffuse demyelinization, and the medulla showed areas of gliosis.

Comment: The patient developed severe, progressive myasthenia gravis six months after surgical removal of a carcinoma of the soft palate with no residual tumor evident at death.

Case 9 — Bowen's Disease

Left cervical adenopathy was the presenting complaint in this 66-year-old man who came for examination in May, 1964. A skin lesion removed six months before showed Bowen's disease. Cervical node biopsy showed metastatic carcinoma which was felt by the pathologist to originate in the thyroid gland. Radical neck dissection and left thyroidectomy showed more metastatic tumor but no primary lesion. There was increasing fatigue and in January, 1965, a prostatic mass became evident. As a needle biopsy showed carcinoma of the prostate, bilateral orchiectomy was done and oral estrogen therapy instituted.

Comment: A diligent search for cancer should be made when Bowen's disease is found, because one in three patients will have internal malignancy.

Case 10 — Basal Cell Carcinoma

This 75-year-old male was admitted to the hospital on April 30, 1965, because of abdominal pain and an epigastric mass. There was past history of pulmonary and laryngeal tuberculosis, Addison's disease, gastrectomy for ulcer, radiographic evidence of probable diverticulitis, and basal-cell carcinoma removed from the back in 1962. Alkaline phosphatase was elevated to 23 King-Armstrong units. Liver biopsy using the Menghini needle was negative. Removal of a suspicious back lesion showed a second basal-cell carcinoma. Surgical exploration revealed metastatic carcinoma of the liver probably originating in the colon.

Comment: Two basal-cell carcinomas preceded the finding of metastatic carcinoma in the liver felt to originate in the colon which had the radiographic appearance of diverticulitis.

Case 11 — Pruritus

This 77-year-old man was found to have pernicious anemia in 1958. He soon developed pruritus which was persistent and bothersome and thought by another physician to be related to liver and vitamin B_{12} injections. In 1961 he was referred to a dermatologist who felt he had senescent pruritus. Increasing weakness and ataxia occurred. Physical examination was negative except for a two-centimeter mass above the left clavicle. As his condition rapidly deteriorated, he could not have diagnostic studies, and he expired February 3, 1962.

Autopsy showed a malignant lymphoma of the Hodgkin's type involving the mediastinal and cervical lymph nodes, spleen, pancreas, and retroperitoneal areas. Arteriosclerosis and encephalomalacia were present.

Comment: Pruritus present for four years was erroneously considered to be an effect of liver injections or senility when it was an apparent earmark of lymphoma.

Case 12 — Pruritus

This patient, who was a 42-year-old housewife, expired October 11, 1964, from longstanding Hodgkin's disease. She was referred in November, 1959, because of general itching and burning of the skin. In 1939 a neck node biopsy showed Hodgkin's disease. In the next 20 years she was treated only with x-ray therapy directed to evident lymph node enlargement. Fifteen courses of radiation were given to the neck, mediastinum, abdomen including pelvis, and inguinal nodes. Nitrogen mustard helped the pruritus. Herpes zoster occurred in September, 1961. Liver involvement became evident in February, 1962, with alkaline phosphatase of 111 King-Armstrong units and bromsulphalein retention of 27%. Various types of chemotherapy were used with little success. Anemia became an increasing problem and was treated with iron and corticosteroids. Back pain occurred and an x-ray in January, 1964, showed sclerosis of the lumbar vertebra consistent with Hodgkin's disease. In March, 1964, weakness of the limbs increased so that it was difficult for the patient to stand or walk. Electromyography showed scattered neuropathic polyphasic units in the right arm and both legs consistent with peripheral neuritis. A gastric ulcer occurred in June of 1964. In the six months prior to death moderate hypertension developed. Increasing cachexia and ascites occurred before death.

Autopsy showed Hodgkin's disease in the only remaining enlarged lymph node found in the femoral region. The liver showed Reed-Sternberg cells. Hemosiderosis was present in the liver and spleen. Contracted kidneys showed microscopic findings consistent with radiation nephritis. Aspiration pneumonia was the terminal event.

Comment: The patient was first seen with pruritus when her Hodgkin's disease of 20 years duration became generalized, possibly from liver involvement. Aside from pruritus, other systemic signs of malignancy included herpes zoster, anemia, peripheral neuritis, hypertension presumably from radiation nephritis, and cachexia.

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11-165 May be secured from the author or the reprints.

The duty of the physician is to cool what is hot, to warm what is cold, to dry what is moist, and to moisten what is dry. He should look upon the patient as a besieged city, and try to rescue him with every means that art and science places at his command. The physician should be an inventor, and think out new ways and means by which the cure of the patient's affection and the relief of his symptoms may be brought about.

— **Alexander of Tralles (525?-605?)**

The Superior Man — Confucius (551-479 B.C.)

The superior man blames himself; the inferior man blames others.

Men, like bullets, go farthest when they are smoothest. — J. P. Richter

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Precautions: Careful supervision of dose and amounts prescribed is advised. Consider possibility of dependence, particularly in patients with history of drug or alcohol addiction; withdraw gradually after use for weeks or months at excessive dosage. Abrupt withdrawal may precipitate recurrence of preexisting symptoms, or withdrawal reactions including, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, the dose should be reduced and operation of motor vehicles or machinery or other activity requiring alertness should be avoided if these symptoms are present. Effects of excessive alcohol may possibly be increased by meprobamate. Grand mal seizures may be precipitated in persons suffering from both grand and petit mal. Prescribe cautiously and in small quantities to patients with suicidal tendencies.

Side effects: Drowsiness may occur and, rarely, ataxia, usually controlled by decreasing the dose. Allergic or idiosyncratic reactions are rare, generally developing after one to four doses. Mild reactions are characterized by an urticarial or erythematous, maculopapular rash. Acute nonthrombocytopenic purpura with peripheral edema and fever, transient leukopenia, and a single case of fatal bullous dermatitis after administration of meprobamate and prednisolone have been reported. More severe and very rare cases of hypersensitivity may produce fever, chills, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, anaphylaxis, stomatitis and proctitis. Treatment should be symptomatic in such cases, and the drug should not be reinstituted. Isolated cases of agranulocytosis, thrombocytopenic purpura, and a single fatal instance of aplastic anemia have been reported, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity has been reported, usually after excessive meprobamate dosage. Suicidal attempts may produce lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

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Abstracts, Briefs and Commentaries

HEMANGIOMA OF THE STOMACH

A Cause of Ulcer and of Gastric Hemorrhage

According to the literature, hemangioma of the stomach is so rare that only a few cases are on record. It is said to be more uncommon than in other parts of the gastrointestinal tract. The authors intend to shake the assumption that the condition is so rare and, if possible, throw some light on the mystery of the numerous cases of gastric hemorrhage of obscure cause which constitute perhaps up to 20% of all gastric hemorrhages. The very few gastric hemangiomas on record seem to have been true tumors, true new growths, either diffusely infiltrating or limited, frequently polypous, cavernous hemangiomas protruding above the level of the surrounding area and therefore usually demonstrable by x-ray.

The authors speak of changes in the gastric wall as cavernous phlebectasia but prefer the term hemangioma. "The vascular changes present themselves as small patches, 3 to 5 mm. in the mucosa, of a reddish-blue color, on or very slightly above the mucosal level." Histologically, they consist of densely placed, large, blood-filled vascular lumina, predominantly venous.

Case Reports

Case 1

A woman aged 46, previously in good health, had five episodes of gastric hemorrhage and melena, preceded by mild pressure pain in the epigastrium. It had been impossible to demonstrate the cause of bleeding. Radiography showed no abnormalities. Laboratory revealed only anemia. Gastroscopy showed an injected gastric mucosa. Close to the angular notch on the anterior aspect of the stomach there was "a small, slightly prominent area the size of half a pea which grossly suggested a hemangioma." There was also a second, smaller, similar area more proximally located. One month later the larger area under the gastroscope presented the appearance of a superficial ulcer with injected, slightly raised edges. Radiology again gave no conclusive result. A Bilroth I operation was performed, and a small ulcer was found at the site demonstrated through the gastroscope. The histological diagnosis was gastric ulcer, hemangioma of the gastric wall. During surgery several hemangiomas of sizes up to a walnut were found in the liver.

Case 2

A man aged 54 with four episodes of melena and severe anemia over six years had negative x-rays. A laparotomy with gastrostomy was negative. Two small typical hemangiomas were found in the small intestine. One year later he had another attack of melena and severe anemia. Gastroscopy revealed three or four hemangiomas on the anterior wall of the stomach. One, raised and cone shaped, had a small lump of

Continued

fibrin on top. X-ray showed an irregular mucosal pattern. A Bilroth I resection was done. At the suspected site three collapsed areas suggesting hemangiomas up to pea size without ulcer formation were found. Histological report: Fairly widespread hemangiomatous lesions in the submucosa.

Case 3

A male aged 46 had a six-year history of dyspeptic complaints. Examination was essentially negative. One year later he gave a history of profuse hematemesis and anemia, and eight months later he again had hematemesis in Holland. He was transferred to the authors in Finland. X-ray examination revealed a polypous lesion, possibly a hemangioma. Gastroscopy revealed three to four dark red, slightly elevated areas, the largest 1 cm. in diameter. A Bilroth I resection was performed. The specimen showed three small red, slightly retracted areas. Histological examination: "Stomach with angiomatous areas in the submucosa, mucosal bleeding, erosion, and scar."

Case 4

A male had a history of 10 years dyspepsia. X-ray showed a duodenal ulcer. About two years later, after more bleeding, x-ray was repeated and again reported to show a duodenal ulcer. No gastroscopy was done, but a Bilroth II operation was performed. There was scarring in the pyloric region but no recent ulcer to account for his bleeding. In the proximal stomach, reddish areas suggesting hemangiomas were found at surgery. A Bilroth II operation was again performed, disclosing hemangiomas on the liver as well as on the patient's forehead. The histologist's report indicated scarring of the duodenum. The hemangioma-like area of the stomach showed densely arranged vessels which in places occupied the entire space between the mucosa and the muscularis, where the mucosa was thin. One area showed bleeding in the mucosa at the margin of the vascular area.

Cases 5, 6, and 7 were not operated upon, but in Case 5 gastroscopy revealed four small hemangioma-like areas. He had been admitted three times for melena.

Case 6 also showed on gastroscopic examination a dark red, hemangioma-like area. He had had occasional hematemesis, melena, and anemia.

Case 7, a female of 59 years, with 20 years of gastric complaints, entered the hospital with profuse hematemesis, melena, and anemia. X-ray and laboratory examinations were essentially negative. Gastroscopy revealed two hemangioma-like areas.

In two years the authors found or diagnosed hemangiomas (cavernous phlebectasias) in seven patients, six of whom were diagnosed by gastroscopy. Four underwent surgery, and hemangiomas were found at the site observed at gastroscopy and were confirmed by histology. Unlike ordinary ulcer hemorrhages, bleeding stopped each time without emergency surgery. This, the authors state, accords with venous bleeding and also with the fact that relief has occurred following gastric resection, when no cause for bleeding was found, in so called "blind cases." Several authors have tried to find a relation between hemangiomas in the skin and in the intestinal tract. Berlyne and Berlyne are quoted as saying that in gastrointestinal bleeding of obscure causes, cavernous hemangiomas in the skin suggest that similar lesions may be present in the bowel and be responsible for the blood loss. Two of their seven patients had hemangiomas of the skin.

Gins et al. presented results of a study of surgically removed stomachs before the clinical congress of the American College of Surgeons in 1963. They could identify three types of vascular alterations: "nests of vessels" in a tangled network of thick-walled vessels in the scar tissue beneath the ulcer, found in gastric as well as duodenal ulcers to which they are not secondary, as frequently assumed. The ulcer may be related to the changed vessels of the stomach or duodenal wall. Possibly we are faced with a so-far unheeded cause of ulcerogenesis in the stomach. Findings indicate these vascular changes in the stomach partially explain the frequency of severe gastric hemorrhages of obscure cause.

None of the operated patients in their series has had gastric hemorrhage since surgery.

Comment: This report is unusual and interesting. The diagnoses via the gastroscope, when x-ray and laboratory studies were unrevealing, is unusual. Although the results are significant, this series is too small to establish positive conclusions. The authors are to be complimented on this presentation.

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CHILDHOOD LOSS OF A PARENT

In 1954, 11,379 Minnesota school children were evaluated by means of the Minnesota Multiphasic Personality Inventory, and in 1957 a follow-up survey was made. Starke R. Hathaway and Elio Monachesi reported on preliminary results in *Adolescent Personality and Behavior,* published by the University of Minnesota Press in 1963. Re-evaluation of the data in terms of the relation between delinquency and socioeconomic status, family stability, and intelligence has now been summarized by Dr. Gregory. Analysis showed that delinquency was more frequent in children who had lost a parent of the same sex, whether by death, divorce, or separation, and that delinquent acts were more common in children from the lowest socioeconomic strata. However, farm children, who committed fewer delinquent acts than city children of comparable economic status, were exceptions to the latter finding. It was also noted that children from the lowest socioeconomic strata who were also of low intelligence dropped out of school more frequently than the average for the general population and that children who had lost a parent of the same sex were also more likely to leave school prematurely, regardless of their intelligence or economic circumstances. Thus, one of the important findings of this study was that the parent of the same sex as the child was crucial in the child's social development, especially in the prevention of delinquency and academic failure. The reasons for this parent's importance are probably manifold, but current thinking suggests that the most crucial one is that he provides the model on which the child bases his identity and aspirations.

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Gregory, I.: Anterospective Data Following Childhood Loss of a Parent. Arch Gen Psychiat 13:99, 1965.

SPONTANEOUS PNEUMOTHORAX

Two hundred consecutive cases of benign, nontraumatic, nontuberculous spontaneous pneumothorax, unassociated with other pulmonary diseases such as pneumonia or tumor are presented. Nearly all were men, and 80% were under 40 years of age. Right and left sides were affected equally. The median time for re-expansion of the collapsed lung was 4 weeks in the nonsurgical group, 3 weeks in the repeated needle aspiration group, and 2 weeks in a small group treated with intrapleural catheter.

Journal of the American Medical Association
Courtesy of References and Reviews

Hyde, L.: Dis Chest 43:476, 1963.

SHELLAC BEZOAR OF THE STOMACH ASSOCIATED WITH OBSTRUCTION OF THE SMALL INTESTINE

Bezoar is a term applied to concretions of various foreign or intrinsic substances found in the stomach and intestine of both men and animals. They are classified as:

1. Trichobezoar — composed almost entirely of ingested hair.
2. Phytobezoar — composed largely of vegetable matter.
3. Concretions — rare types, occurring in people who ingest furniture polish, resins, paraffin, asphalt, bismuth, gums, etc.

DeBakey and Ochsner, through an exhaustive search of the world literature, collected 303 cases of bezoars and added eight of their own. The reported cases were 172 in #1, 126 in #2, and 13 in #3. Of the 13 cases in #3, eight were composed of shellac. Shellac bezoars are very rare. Added are a few more reported in Norway, Germany, Russia, and Australia.

Case Report:

A 36-year-old worker, a drunkard accustomed to alcohol in any form, started drinking various kinds of alcoholic solutions of shellac four years ago. He usually precipitated and removed most of the shellac by adding table salt before drinking the liquid portion. This was while he was in prison, where there was no alcohol available. On discharge he again drank ethyl alcohol for one week and then an average of half a liter per day of alcoholic solution of shellac for two weeks.

He then began to have stomach ache and a sensation of a large mass in his stomach. He developed a sudden attack of pain followed by nausea and vomiting and was admitted to the hospital, acutely ill with marked abdominal distension and active peristalic sounds. Gaseous distension of the small bowel suggested obstruction.

On operation a foreign body impacted in the mid-ileum was removed, consisting of a large, ovoid, brownish, coarsely-spongy structure 7 cm. at its greatest diameter. A second mass, 40 cm. long, forming a true cast of the stomach and weighing 900 gm., was removed. The specimens at first were soft but hardened rapidly and showed fissuring of their surfaces. The surface was bright yellow and glossy, but the center was black and spongy. Both concretions consisted of shellac. The smaller body removed from the ileum was a fragment from the larger mass. There were no changes in the gastric wall. The patient made an uneventful recovery.

It is noted that when the alcohol is absorbed, the shellac, which is not soluble in gastric secretions, is precipitated out and forms the bezoar. Important factors are the craving for alcohol and the fact that in most instances the subjects have worked in trades in which alcoholic solutions of shellac are used in considerable amounts.

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Valtonen, Erkki J.: The Dept. of Surgery, Malmi City Hospital, Helsinki, Finland. Acta Chir Scand 129:567, 1965.

FECALITHS OF THE APPENDIX

The records of 100 patients with appendicitis and 100 with uninflamed appendix were studied and compared as to the incidence of fecaliths. In the first group there were 17 fecaliths, of which 12 had been seen by roentgenographic examination. There were four fecaliths in the uninflamed-appendix series, and one of them had been detected radiologically. This difference of incidence in the two series suggests that fecaliths are associated with acute appendicitis about 10 to 12 times as often as with uninflamed appendices, and that the discovery of a radiopaque fecalith indicates at least a 90% chance of the presence of acute appendicitis. The characteristic roentgenographic finding is the presence of one or more laminated densities, 5 to 20 mm. in diameter, usually located within 15 cm. radius of the mid-point of the right iliac crest. Most of these densities are oval, but other shapes are often observed. The lamination may be poorly visualized, especially when the fecalith is superimposed on bone. It is recommended that immediate surgery should be performed when a fecalith is accidentally found in patients with asymptomatic appendix, especially among children. The presence of a fecalith increases the probability of complication by gangrene and perforation, as happened in 12 cases of the acute appendicitis series in this study. Given the diagnostic specificity of the fecalith sign, routine abdominal roentgenography is advisable whenever appendicitis is suspected.

Courtesy of References and Reviews
Journal of the American Medical Association

Faegenburg, D.: Amer J Roentgenol 89:752, 1963.

REMOVAL OF OVARIES WITH HYSTERECTOMY

There are a number of sequellae that may occur as a result of estrogen deficiency: e.g., negative nitrogen balance, hypocholesterinemia with an increase in coronary atherosclerosis, hypertension, osteoporosis, atrophy of the vaginal wall, senile vaginitis and its concomitant symptoms, and urinary incontinence as a result of atrophy of the muscles and connective tissues supporting the bladder.

Despite this, Fugo points out the possibility of developing carcinoma in the remaining ovaries after hysterectomy, and he recommends salpingo-oophorectomy in all cases where hysterectomy is indicated. He further recommends that estrogen therapy be administered in all of these women, even until old age, in order to prevent metabolic and atrophic changes which are characteristic of a lack of estrogen. He states that the danger of prolonged estrogen administration is minimal.

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Fugo, Nicholas W.: Should the Ovaries Be Conserved at Hysterectomy. W Virginia Med J 61:247, 1965.

SLEEP PARALYSIS

The literature suggests that sleep paralysis is an unusual phenomenon that occurs chiefly in narcoleptics and cataleptics. The author, however, gained the impression that it is by no means rare; that it is not usually associated with narcolepsy or catalepsy; that people do not usually consult doctors about it; and that many regard it as a personal idiosyncrasy best kept to themselves. The author investigated the incidence of sleep paralysis among 52 freshman medical students who could be regarded as generally healthy. He found that 8 (or 15.4%) responding to a questionnaire had experienced sleep paralysis. He compares his findings with those of a study by Gorde on 359 subjects, of both sexes (mostly medical and nursing students). This study had disclosed an incidence of 4.7%,

Continued

and also that the condition was 4 times more frequent in males than in females. None of those with sleep paralysis were found to be narcoleptic or cataleptic. The author likewise found no association between sleep paralysis and narcolepsy or catalepsy. Although the majority of those with sleep paralysis experience anxiety during the attacks, the remaining patients tend to feel a definitely pleasant sensation. A variety of other interesting subjective experiences may accompany sleep paralysis, some of which might be termed "depersonalization."

Courtesy of References and Reviews
Journal of the American Medical Association

Everett, H.: J Nerv Ment Dis 136:283, 1963.

SPERMATOCELE

Spermatoceles are single, multilocular or multiple retention cysts of ductuli efferentes which may grow large enough to require surgical removal. Between dense fibroelastic membrane of the spermatocele sac and the cremaster, a nearly avascular cleavage plane has regularly been observed, the use of which permits separation of the lesion from surrounding tissue with minimal bleeding, trauma, or postoperative reaction. Complete removal of multiple or multilocular cystic elements favors nonrecurrence. Reconstruction of the cremaster restores normal activity of this muscle.

Courtesy of References and Reviews
Journal of the American Medical Association

Clarke, B., Bamford, S., and Gherardi, G.: Arch Surg 86:351, 1963.

Medicine

Looking out on the present state and prospect of medicine, it is obvious that its future work will be mainly to prevent and stop the beginning of disease — to take good order that it shall not come, and if it do come, to prevent functional disorder from lapsing into fixed disease, which must be given over either to the surgeon's knife or to the shears of Atropos;* for to despise the little things of functional disorder is to fall by little and little into organic disease. . . . If mankind is to be perfected, the means of perfecting it must be sought in the medical sciences.

— Dr. Maudsley, President of the Section of Medicine,
to the British Medical Association, 1905.

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*Atropos — Greek goddess of fate who terminates life.

Pulheems

A system of medical classification for recording the physical and mental status of recruits in the British fighting services, representing: P, physical capacity; U, upper limbs; L, lower limbs; H, hearing (acuity); EE, eyesight (visual acuity); M, mental capacity; S, stability (emotional).

Recent advances in communications have been spectacular. Yet there's still a lot to be said for the wink. — Changing Times

Book Reviews

A good book is the very essence of a good man. — His virtues survive in it, while the foibles and faults of his actual life are forgotten. — All the goodly company of the excellent and great sit around my table, or look down on me from yonder shelves, waiting patiently to answer my questions and enrich me with their wisdom. A precious book is a foretaste of immortality. — T. L. Cuyler

DEPRESSIVE STATES: A PHARMACOTHERAPEUTIC STUDY — by Anthony Hordern, M.D., Charles C Thomas Publishers, Springfield, Ill., 1965. 166 pages.

Dr. Hordern, at present a consultant psychiatrist at the Kings College Hospital of London, has written a scholarly review of depression and, in addition, has provided a well-designed study of an antidepressant drug. He begins his book with a discussion of the depressive syndromes, which includes a critical review of the epidemiology, phenomenology, social consequences, and complications of depression. He points out the ubiquity of depressive illness in all areas of medical practice, and he gives a careful and well-documented review of the physical therapies of depression, including electroshock, prefrontal lobotomy, and antidepressant drugs.

The greater part of the book comprises a detailed discussion of a controlled investigation of imipramine and amitriptyline. The procedures, methods, and means of statistical analysis are well described and contribute a more-than-adequate model for controlled evaluations of antidepressant agents. The statistical analyses of drug efficacy, of symptom constellations, of interaction between symptoms, and of factors like age are especially noteworthy.

Generally, the book is well-written and lucid. However, the author does include the bibliographic names in the text of the book, which makes for slow and difficult reading. The drug study described is worth careful examination by anyone interested in psychopharmacologic research, and the conclusions are certainly of value to all clinicians who treat depressed patients. Dr. Hordern's statements about the relative efficacy of amitriptyline cannot be questioned on the basis of his data, but it is possible that other therapies may be better than he implies. Also, since he did not include a placebo group in his investigation, his generalizations about the effectiveness of antidepressant drugs are open to criticism. While it is true that previous investigations suggest the superiority of both imipramine and amitriptyline over placebo, it is also true that one is more confident of statements about a drug's effectiveness in any study when a placebo control is included. Perhaps this is a small point, and it is surely one which many experienced investigators would dispute, but medical history strongly supports cautious skepticism for all therapies whose value has not been proven by time and by many controlled investigations.

In conclusion, Dr. Hordern's book will be primarily valuable to psychiatrists and clinical investigators, although it possesses sufficient clinical material to be of interest to any clinician who treats depressive illnesses. The author's review of physical therapies in depression is well done and could serve as a primer for those who are unfamiliar with the literature on these therapies.

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St. Paul, Minnesota

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*Assistant Professor, Department of Psychiatry and Neurology, University of Minnesota and St. Paul — Ramsey Hospital.

FROM AUSCULTATION TO PHONOCARDIOGRAPHY — Aldo A. Luisada, C. V. Mosby Co., St. Louis, Missouri; 1965, 314 pages; price $17.75.

Luisada has long been known as one of the leaders in the field of heart sounds and their graphic representation. This work is a thorough study of phonocardiographic technique and its value as an adjunct and corrective to auscultation. For the clinical cardiologist and for all physicians who examine hearts there is much to learn from this volume.

Luisada divided the precordium into overlapping areas of auscultation: right atrial, right ventricular, aortic, and pulmonic areas. However, there are better landmarks that can be used to designate where a sound is heard. Luisada places one of the most important sounds in cardiac auscultation, the mitral diastolic rumble, in the area between the apex and the (left) sternal border. This murmur, however, is usually best heard exactly at the apex or slightly lateral to it and often only in that region.

The greatest value of the phonocardiogram, as Luisada repeatedly emphasizes, is its precise timing of audible events in the heart cycle. Clinicians can learn much about auscultation from phonocardiography. The phonocardiogram can often be helpful to the clinician in diagnosis.

Reuben Berman, M.D.
Minneapolis, Minnesota

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Special Article

The Minnesota Breast Cancer Clinics

CARCINOMA OF THE breast continues to be the most common fatal neoplasm of women. For most patients with this disease it is not until after the appearance of symptoms that the diagnosis is made and, more often than not, by this time the tumor is no longer localized to the breast and already presents overt evidence of spread to lymph nodes or other areas.[1] Although improved surgical techniques, chemotherapy, and radiation treatment have brightened the outlook for most cancer patients during the past 25 years, survival rates for patients with neoplasms of the breast continue to be disappointing. Presently more than half of the women found to have breast cancers can anticipate eventual death from the disease, and the outlook for 10-year survival is probably less than 40%.[2]

Improving the prognosis for breast cancer patients has been of continuing interest to physicians. The conventional treatment for this disease has been surgical, and for the past 70 years or so the conventional operation has been the so-called Halsted mastectomy. Recently, with the hopeful anticipation of achieving more complete extirpation of a greater proportion of nonlocalized breast cancers, several more extensive operative procedures have been described and, over the years, a number have undergone clinical evaluation. None of the more radical operations, unfortunately, has demonstrated a superiority in long-term survivals; in consequence, none has found wide application or acceptance. In other quarters the limited operation of simple mastectomy, accompanied by radiation therapy, has been advised. Somewhat surprisingly, recently reported survival rates following these more limited operations have differed very little from those reported for the Halsted procedure. Final evaluation of the results of the more restricted operations, however, will probably require several years.

Stimulated by the encouraging results of the widespread use of the Papanicolaou smear, increasing emphasis has been placed on the early detection of cancer. Studies of patients with breast cancers seen at the University of Minnesota Cancer Detection Center, for example, have shown that when the cancers were detected by the physician during routine annual examination, rather than

TABLE 1

Minnesota Breast Examination Clinics
1961-1965

	Crookston	Fergus Falls	Owatonna	Virginia Hibbing	Cambridge	All
Patients examined	1,122	1,072	1,143	1,209	892	5,438
Breast abnormalities found	48	85	62	117	63	375
% with breast abnormalities	4.3%	7.9%	5.4%	9.7%	7.1%	6.9%
Participating physicians	17	36	39	47	22	161
Participating nurses	50	32	40	40	26	188

Continued

found by the patient herself, the majority have had no evidence of spread beyond the breast at the time of therapy; that more than 90% of the patients with breast cancers found at the Center have been five-year survivors; and that survival at both five and 10 years has been 100% of that statistically anticipated for similar patients without breast cancer.[3]

Breast Clinics

To emphasize the importance of early detection of breast cancer, the Minnesota Division of the American Cancer Society, the Cancer Committee of the Minnesota State Medical Association, Minnesota Department of Health, and the Cancer Detection Center at the University formulated a program of breast clinics to be conducted in conjunction with professional and lay education programs. Since 1961 five such clinics have been held throughout the state.

Sponsoring Organizations

Organization and operation of the breast cancer clinics have emphasized participation at the local level. The sponsoring organizations usually have been the county medical societies, with the assistance and cooperation of members of the district units of the American Cancer Society. Local volunteers, with the coordinating help of the Minnesota Division of the Cancer Society, have been responsible for the multitude of details of arrangements and scheduling required for the successful operation of such clinics.

Education Seminar

Preceding each clinic a cancer education seminar was held for physicians of the area. The programs were presented by a faculty of University of Minnesota staff members and clinical affiliates. Methods and results of early cancer detection, lectures concerning diagnosis and treatment of neoplasms of the breast, uterus, bowel, prostate gland, lung, and other organs, and demonstrations of the techniques of breast examination comprised the seminars.

The examination clinics, usually conducted the following day, were staffed primarily by the physicians of the area. Members of the University staff, including participants in the seminar, were available for consultation and assistance. The women who underwent the breast examinations were residents of the local areas, 35 years of age or older. Participation was on the basis of interest, and no effort was made to limit the group to asymptomatic persons. Women were requested to preregister with the local unit of the American Cancer Society. An additional small number of other women were also accepted for examination after registering at the time of the clinic.

Referral to Attending Physician

The examinations at the clinics were comprised of routine methods of physical diagnosis. Mammography and other x-ray examinations were not undertaken. No treatment was performed. Breast abnormalities which were found and questionable conditions for which re-examination appeared to be indicated were reported to the private physicians designated by the patients. Those found to have abnormalities of the breast were urged to consult their own physician for further examination or evaluation. The follow-up information in this report was ob-

TABLE 2

Age Distribution of Women Examined
Minnesota Breast Examination Clinics

Age	Less than 35	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Un-known	Total
No. Patients	51	831	915	991	808	603	409	287	133	32	9	2	367	5,438
% Total	0.8	15.2	17.7	18.2	14.9	11.0	7.4	5.2	2.3	0.5	0.2	-	6.6	100%

tained from the private physicians four months to one year after each clinic.

Results

The five breast cancer clinics held in Minnesota since 1961 were conducted in Crookston, Fergus Falls, Owatonna, Virginia-Hibbing, and Cambridge (Table 1). The age distribution of the patients examined is shown in Table 2. Based on U. S. Public Health Service estimates,[4] 7.8 breast cancers could be expected among 5,438 women of this age distribution.

Incidence of Abnormality

Of the 5,438 women examined, 375 (or

TABLE 3

Minnesota Breast Examination Clinics
1961-1965
375 Breast Abnormalities Found at Breast Clinics

	Crookston	Fergus Falls	Owatonna	Hibbing	Cambridge	All
Breast abnormality at clinic	48	85	62	117	63	375
Failed re-examination	5	13	4	25	18	65
Returned for re-examination	43	72	58	92	45	310
No abnormality found	15	30	25	50	12	132
% No abnormality	35%	42%	43%	54%	27%	43%
Abnormality on re-examination	28	42	33	42	33	178
% Abnormality	65%	58%	57%	46%	73%	57%

TABLE 4

Minnesota Breast Examination Clinics
1961-1965
178 Breast Abnormalities
"Confirmed" on Re-Examination by Private Physicians

	Crookston	Fergus Falls	Owatonna	Virginia Hibbing	Cambridge	All
All patients seen at clinics	1,122	1,072	1,143	1,209	892	5,438
Breast abnormality on re-examination	28	42	33	42	33	178
% of all seen at clinics	2.5%	3.9%	2.9%	3.5%	3.7%	3.3%
Adenocarcinoma	4	2	1	-	1	8
Fibrocystic disease	15	36	27	37	23	138
Lipoma	6	-	-	1	3	10
Fibroadenoma	2	-	1	-	4	7
Calcified adenoma	-	2	-	-	-	2
Ductal hypertrophy	2	1	-	-	-	3
Old breast scar	-	-	2	-	-	2
Ductal papilloma	-	-	-	-	1	1
Lobular hyperplasia	-	-	1	-	-	1
Subareolar fibrosis	-	1	-	-	-	1
Nipple retraction	-	-	-	-	1	1
"Suspicious", but biopsy refused	-	-	1	2	-	3
"Suspicious", but failed re-check	-	-	-	3	-	3

Continued

6.9%) were found by the examining physicians to have breast abnormalities or "suspicious" findings requiring referral to private physicians. Three hundred and ten (83%) of these 375 with abnormalities found at the clinics returned to their physicians for re-evaluation (Table 3). Re-evaluation by their private physicians revealed a definite breast abnormality in 57.6% of the 310 women who returned for examination.

Most Common Abnormality

The most common abnormality found was fibrocystic disease, which accounted for 77.5% of the breast abnormalities present on re-examination (Table 4). Eight cancers of the breast were found (7.8 were expected on the basis of age-specific incidence rates).

TABLE 5

Minnesota Breast Examination Clinics
1961-1965
of Each 1,000 Women Examined at the Clinics

Breast abnormality found at the clinic	69
Returned to private physician for examination	57
Breast abnormality "confirmed" by private physician	33
Fibrocystic disease found by private physician	25
No breast abnormality found by private physician	24
Adenocarcinoma	1.5
Biopsies performed	14

TABLE 6

Minnesota Breast Examination Clinics
1961-1965
Patients Who Returned to Private
Physicians for Examination*
of Each 100 Women with
Abnormalities Who Returned

Abnormality found on re-examination	57.6
Fibrocystic disease	44.4
Lipoma	3.2
Adenoma or fibroadenoma	2.9
Adenocarcinoma	2.6
Other benign breast conditions	2.5
Refused recommended biopsy	1.0
Failed re-check examination	1.0
No abnormality found on re-examination	42.4

*5.7% of all women examined in the clinics; or 83% of all women with abnormalities found in the clinics.

Three patients were found to have an abnormality for which biopsy was recommended but was refused. Another three women were requested by their physicians to return for follow-up examination but failed to do so.

Thus, of each thousand patients examined in the clinics, 69 were found to have breast abnormalities, and 57 of these returned to their private physicians for re-examination (Table 5). In 33 of each 57 (58%) who returned for re-evaluation, a breast abnormality was "confirmed." In 25, fibrocystic disease was diagnosed on re-examination, and in 24, re-examination showed only normal breast. Or, of each 100 patients examined by the private physicians for breast abnormalities as a result of the clinics, 44.4 had lesions which were diagnosed as fibrocystic disease; in 42.4 no abnormality was found; 3.2 had lipomas; 2.9 had fibromas or fibroadenomas; 2.6 were found to have cancers; 1.0 refused recommended biopsy; 1.0 failed recommended follow-up examination; and 2.5 had other benign breast conditions (Table 6).

Discussion

Although carcinoma of the breast is a relatively frequent cause of death in this country, accounting for three of each 100 deaths which occur in the female and for nearly 20% of cancer deaths in women, at any given time the prevalence rate of previously undetected breast neoplasms is substantially lower. In fact, the eight women with cancers found in the clinics included two with previously recognized lesions: one of the women had already consulted her own physician and was aware of the probable diagnosis; and the other had refused therapy for an advanced, ulcerating lesion. Two additional cancers not suspected in the clinic were detected as a direct result of referral of patients to their private physicians for further evaluation, i.e., one of the cervix and the other of the contralateral breast; both of these patients had lesions which were detected early, the prognosis for which should be excellent.

Thus the merit of regular periodic breast examinations is emphasized; and, although only a modest number of detectable but previously undiagnosed breast cancers appear to exist at any one time, these lesions seem to occur at a relatively constant rate in the population; so that at the present rate of occurrence at least one of each 20 women can be anticipated eventually to develop this disease. While the actual number of breast cancers detected was small, the acquainting of several thousand women with the ease and simplicity of breast examinations, the re-enforcement of the concept of the merit as well as the acceptability of routine examinations of asymptomatic persons, and the making known to physicians and lay persons alike the order of magnitude of the potential improvement in prognosis for breast cancers detected while yet asymptomatic, were worthy objectives of this educational venture.

Summary

To help acquaint physicians and lay persons with both the methods and the importance of the early detection of breast cancer, five breast cancer education-examination clinics and seminars have been held since 1961. A total of 5,438 women were examined. About 6% of the women seen at the clinics were re-evaluated by their local physicians upon the recommendation of the clinic examiners. More than half of the patients who returned to their private doctors were found on re-examination to have definite breast abnormalities, and about 44% of those with "confirmed" abnormalities underwent breast biopsies. The lesion most commonly detected was fibrocystic disease, which was found in 25 of each 1,000 women seen in the clinics and accounted for 77% of the "confirmed" breast abnormalities. Eight breast cancers were detected (1.5 cancers per 1,000 women examined).

The ease and simplicity as well as the importance of breast examinations in asymptomatic persons were demonstrated to thousands of women and to hundreds of physicians and nurses in the several areas in the state.

Victor A. Gilbertsen, M.D.*
J. Jeffrey McCullough, M.D.**
Donald E. Stewart, M.D.†
Lyle Hay, M.D.‡
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This study was supported by the Minnesota Division of the American Cancer Society and the Minnesota State Department of Health, and had the approval and endorsement of the Cancer Committee of the Minnesota State Medical Association.

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Those who want to put the brakes on government spending should find out how long it's been since the brakes were tested. — New York Sun

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It cost Columbus $7,250 to discover America — a small fraction of what it costs a Congressional Committee to discover a few facts. — Grit

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History of Medicine

The Discovery of Insulin

The first description of diabetes dates back to about 1500 B.C., as presented in the Papyrus Ebers, wherein the symptoms of the disease, which we now call diabetes were described. These symptoms were later described in greater detail by the encyclopedist Celsus at the time of Julius Caesar.

In 1869 an anatomist, Dr. Paul Langerhans, though not realizing any relationship between the pancreas and diabetes, gave us an anatomical description of the pancreatic tissue by noting certain microscopic nests of cells imbedded therein, which are now known as the Islets of Langerhans.

The true nature of the relationship of the pancreas to diabetes was not identified until 1889, when von Mering and Minkowski demonstrated that the removal of the pancreas in dogs resulted in diabetes, although this still did not clarify which of the two types of tissue in the pancreas was responsible for controlling the sugar metabolism.

Little progress was made in the understanding of the relation of the pancreas to diabetes until 1900, when Dr. E. L. Opie of Johns Hopkins University described the presence of pathological changes in the Islets found in cases of diabetes studied at postmortem. Many preceding observers had speculated that a hormone was probably secreted internally by the Islets and carried directly by the blood stream, thus controlling the metabolism of sugar. Attempts had been made to treat diabetics by feeding pancreatic tissue or its extract to the patients, or by injecting the extract. But no satisfactory clinical results were obtained.

It was not until 1922 that any successful treatment for diabetes was finally achieved. A young orthopedic surgeon from New London, Ontario, Dr. Fredrick G. Banting, quite by accident came upon the clue which led him to the discovery of insulin.

In his speech delivered at the dedication ceremony of the new Eli Lilly Research Laboratories in Indianapolis in 1934, Sir Frederick Banting (he had since been knighted for his discovery) tells how this discovery came about. He relates how, after struggling in the practice of orthopedic surgery for several months without success in making a livelihood, he decided to take a part-time position as demonstrator in the department of physiology and anatomy at the University of London, Ontario.

On October 30, 1920, when he was preparing a lecture on the relation of the pancreas to diabetes, there came to his attention an article on the pancreas in the newly-arrived November issue of "Surgery, Gynecology, and Obstetrics." To quote Dr. Banting: "This journal contained an article by Moses Barron, in which he pointed out the analogy between the degenerative changes which followed experimental ligation of the pancreatic duct and that of the blockage of the duct by pancreatic stones.

"After reading the article by Barron, I was unable to sleep." Dr. Banting tells at this point how he jotted down in his notebook: "Ligate pancreatic ducts of dogs, wait six to eight weeks for degeneration, remove the residue and extract."

The next morning he consulted a colleague, on whose advice he went to the University of Toronto, his alma mater, to consult Professor J. J. R.

Continued

Macleod, head of the department of physiology and an authority on carbohydrate metabolism, to obtain facilities necessary to carry out the research he contemplated.

But he got little encouragement from Professor Macleod, who asked him what "he hoped to accomplish, when the best-trained physiologists had not succeeded in establishing or proving that there was an internal secretion of the pancreas." As consultations with other colleagues were equally discouraging, it was decided that Dr. Banting go back to his medical practice and teaching in London, Ontario, to complete the term. After four months he returned to Toronto and asked Macleod to be allowed to tie the pancreatic ducts of a number of dogs.

On May 16, 1921, Banting began his experiments. He was allowed the services of two graduate students, Mr. Best and Mr. Noble, each to give assistance for a period of four weeks. In the talk he gave at Indianapolis, Dr. Banting relates an interesting incident which shows what a significant role fate can sometimes play. Mr. Best and Mr. Noble "tossed a coin to decide who would give the first four weeks, and Mr. Best won the toss. At the end of the four weeks Mr. Noble could not return, and Mr. Best stayed with me and was associated with me throughout the entire work."

The experiments which Dr. Banting and his associates carried on consisted of ligating the pancreatic ducts of the dogs, waiting six weeks for the degeneration and atrophy of the secretory glands which produce the digestive ferments, and watching for the degeneration of the enzymatic secretory glands. The result hoped for was that all this would take place, leaving the Islets of Langerhans intact. And this did actually happen. The experiment of injecting the extract of the degenerated pancreatic tissue had proved a success.

Extracts were then made of the degenerated pancreatic tissue, and after injecting the extract into normal and diabetic dogs, it was found that the blood sugar had actually been lowered.

On January 11, 1922, the extract was first used on patients in the Toronto General Hospital. The treatment of the patients was equally successful. At this point Dr. Macleod, becoming enthusiastic about the results, turned over most of his laboratory staff to the problem.

The task of chemical refinement was assigned to Dr. J. G. Collip, who quickly succeeded in producing a less toxic and more active product. It was later in the spring of 1922 that Dr. Best, because of his experience in chemistry, was able to make possible the production of insulin in larger quantities and still higher purity. However, the product continued to produce sensitization reactions, and it was not before January 1923 that, through the collaboration of the laboratories of Connaught and of Eli Lilly and Company on the production of insulin, the product became stable and pure.

The problem of quantity of insulin production fortunately was solved through chemical experimentation through which it was found that acidified alcohol dissolved the antidiabetic hormone produced by the Islets of Langerhans *without* dissolving the enzymatic secretions of the pancreas.

(To be continued)

Moses Barron, M.D.[*]
Minneapolis, Minnesota

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Excerpts from a Presidents Address*

Ladies and gentlemen of the Minnesota State Medical Society,

I thank you most heartily for the honor you have conferred upon me, and in the discharge of my duties as your presiding officer I will endeavor to act impartially. As a profession it is well for us to stop our scientific labors occasionally and, looking about, see if we have fulfilled our trust to the public and maintained our high position as the most progressive and enlightened of the learned professions.

Let us have the patience of a righteous cause and await this slow but sure progress. It is humiliating to members of our profession to see so many positions of public trust held by irregulars — but we must recollect that the world is not run by the highest thought but by the average intelligence, and the right of the minority to representation is but justice.

Our relations with *the clerical profession* as a whole are satisfactory. There are certain inherent differences between the professions which render a common point of view somewhat difficult. Our profession is nothing if not progressive, and medical history is useful only so far as having led up to the present and as a basis for the future. The theological profession is based upon the past and is history repeating itself with such modifications as have been forced upon it from the outside. They guard a secret trust and view innovation with alarm. The eager striving of the medical profession for the new gives to them an apparently materialistic tendency, while the faith of the clergy is only too often exaggerated into gullibility, and leads them to the recommendation of various patent remedies for the cure of incurable disease, and the endorsement of secret compounds to which they too frequently lend their name and influence. Let us charitably look upon this as merely an evidence of atavism from our common ancestor, the priest physician of the middle ages. These fraternal differences, it is to be hoped, will only cement more closely the hereditary ties and, in the future as in the past, the two professions will go hand in hand.

With *the legal profession* we work in the most perfect harmony outside the courtroom, but as medical witnesses we are an exhibition — a sight for gods and men. The physician is an egotist of necessity. He must give his patients confidence in order to secure that tranquility of mind so necessary for their welfare. — The opinion of a medical witness is based frequently upon technical evidence which cannot be explained to those not educated to his line of thought, and with the hypothetical question the changing of a single word will give grounds for medical experts to honestly differ.

Our relations with *the press* are peculiar but not inharmonious. — As a profession I think sometimes we are a little bit inclined to claim immunity from the common errors and to play something of the oracle. The press hears much about our code of ethics but finds, if our names are found in the paper in the account of an accident or at the bottom of a daily bulletin of our illustrious patients, that our feelings are not so deeply lacerated after all. We must explain to our friends of the pencil that we are human, but that our profession is divine.

We will admit many personal shortcomings but insist that *our code of ethics* is not the superannuated farce they believe it to be, but that it contains the opinion of the profes-

Continued

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*W. J. Mayo, M.D., Transactions of Minnesota State Medical Society, 1894. Obtained through courtesy of Charles G. Sheppard, M.D., Le Sueur, Minn., who's father practiced in Minnesota for more than fifty years.

sion as to how gentlemen should act who hold confidential relations with their patients. This leads me to the prominent question before the American Medical Association: shall we have a change in our code of ethics, leave it alone, or wipe it out utterly. — I see no good reason why we should meddle with it. It simply explains how a gentleman acts while engaged in the practice of medicine.

Pertaining to *personal damage suits* for malpractice — the physician in the course of his whole duty is often exposed to ill timed and often unjust criticism; to attempt to secure special protection from this annoyance is to demand class legislation which would in the long run damage us in public opinion more than we would gain. I believe on the whole that we had best leave this matter to the common justice of the people.

It is a matter of state pride to us to note that in the discussion of some form of public control, our societies have promptly placed themselves in line with the most advanced thought.

Our transactions have been very well presented by the Northwestern Lancet during the past year and our state is to be congratulated upon having so excellent an organ in its midst, and its editors and publishers should be thanked by this society for the literary and artistic merit of its publication; not only in medical literature but in medical education are we to be felicitated.

Our great University medical department from small beginnings has rapidly advanced to a proud position of eminence for which our profession may be justly proud. —

In conclusion I would call your attention to the most excellent scientific program which in itself is an indication of progress and industry of our fellows.

Editor's Note: Doctors! We are still being watched!

Gulliver's Travels — Jonathan Swift

Gulliver — On How to Sue a Neighbor for his Cow

"If my neighbor hath a mind to my cow, he hires a lawyer to prove that he ought to have my cow from me. I must then hire another to defend my right; it being against all rules of law that any man should be allowed to speak for himself. — I, who am the true owner, lie under two great disadvantages. First, my lawyer being practiced almost from his cradle in defending falsehood, is quite out of his element when he would be an advocate for justice —. The second disadvantage is, that my lawyer must proceed with great caution: or else he will be reprimanded by the judges, and abhorred by his brethren, as one who would lessen the practice of the law. And therefore I have but two methods to preserve my cow. The first is, to gain over my adversary's lawyer with a double fee; who will then betray his client, by insinuating that he has justice on his side. The second way is for my lawyer to make my cause appear as unjust as he can; by allowing the cow to belong to my adversary; and if it be skilfully done, will certainly bespeak the favor of the bench.

They never desire to know what claim or title my adversary has to my cow; but whether the said cow were red or black; her horns long or short; whether the field I graze her in be round or square; whether she were milked at home or abroad; what diseases she is subject to, and the like. After which they consult precedents, adjourn the cause from time to time, and in ten, twenty, or thirty years come to an issue."

(To be continued.)

113th Annual Meeting

St. Paul Awaits Minnesota Physicians in 1966

Computer Medicine: Its Application Today and Tomorrow, a subject with an increasing amount of interest among physicians and lay persons alike, will be among the topics presented at the scientific sessions of the 113th Annual Meeting of the Minnesota State Medical Association, May 16 and 17 in St. Paul.

The scientific sessions will be held in the St. Paul Municipal Auditorium and the House of Delegates will convene in the St. Paul Hotel.

The opening scientific session devoted to Computer Medicine, scheduled to begin Monday, May 16, at 9:00 A.M., will feature a presentation by Morris F. Collen, Oakland, California. Doctor Collen is a former Minnesotan, now with the Permanente Medical Group in California. His presentation will be based upon his vast experience using computers extensively in physical examinations and diagnostic tests.

Other general scientific sessions on this year's annual meeting program will be on the subjects of hematology; obstructive respiratory diseases; treatment of burns; respiratory distress syndrome in the newborn; isotopes; hyperthyroidism; prevention of knee injuries; juvenile diabetes; treatment of staph and strep infections and the early recognition and treatment of blindness.

The program on Monday and Tuesday is acceptable for 4½ credit hours by the American Academy of General Practice. In addition, there will be an opportunity for physicians to attend the traditionally popular noon Round Table luncheons Monday and Tuesday at the St. Paul Hotel. The opening round of luncheons will be on the subjects of Fluids in Infancy; The Spiritual Dimension of Suffering; The Use of Saline Solutions in the Treatment of Hemorrhagic and Traumatic Shock; Treatment of Leukemia; Management of

Continued

Emphysema; and Computers in Preventive Medical Research.

Tuesday round table topics are as follows: Prevention and Treatment of Ankle Injuries; Value and Use of the Tonometer; The Brittle Diabetic; Radioactive Isotopes in Clinical Practice; Amniocentesis, A Diagnostic and Therapeutic Tool; and Therapeutic Abortion in General and in Rubella.

Noting the increased interest in Medicine and Religion and the enthusiastic response to this important subject shown at last year's meeting, the Committee on Scientific Assembly is pleased to announce that a panel on "The Dying and the Dead" has been scheduled for Monday at 2:30 P.M. Panelists will include: Harold W. Hermann, M.D., Minneapolis, as moderator; Bishop James P. Shannon, St. Paul; Reverend Elmer Hjortland, Oak Park, Illinois; and Rabbi Albert G. Minda, Minneapolis.

Organizations and specialty groups planning events in conjunction with this meeting include the Minnesota Radiological Society, Minnesota Chapter of the American Academy of Pediatrics, Twin Cities Diabetes Association, Minnesota Chapter, American College of Chest Physicians, Minnesota Academy of Ophthalmology and Otolaryngology and The Medical Women's Association. The Minnesota Academy of General Practice will hold its Annual Banquet Monday evening. The Annual Banquet of the Minnesota State Medical Association will be held Tuesday evening. The new members, officers and delegates dinner at 6:00 P.M. will follow the opening session of the House of Delegates Sunday, May 15. The House of Delegates will convene Sunday, May 15, at 2:00 P.M. and again Tuesday, May 17, at 9:00 A.M.

The concluding scientific session on Tuesday at 4:00 P.M. will feature an obstetrics and gynecology seminar. Seminar topics scheduled are: Endometriosis, the Conservative vs. the Radical Surgical Treatment; and Early Invasive Carcinoma of the Cervix.

An impressive selection of scientific and technical exhibits will be on display Monday and Tuesday at the St. Paul Auditorium. Physicians are invited to visit the exhibits and to express their appreciation to the technical exhibitors whose participation annually helps to make this meeting possible.

The official program including detailed information about scientific, business and social activities will be mailed to all members. Kindly check the official Annual Meeting program for complete details.

Scientific Program
Saint Paul Auditorium

MONDAY MORNING, MAY 16, 1966

The program on Monday is acceptable for 4½ accredited hours by the American Academy of General Practice.

A.M. Visit scientific and technical exhibits

9:00 **COMPUTER MEDICINE: ITS APPLICATION TODAY AND TOMORROW**
Morris F. Collen, Oakland, California

9:40 **WHAT'S NEW IN HEMATOLOGY?**
A. B. Hagedorn, Rochester

10:15 Visit scientific and technical exhibits

11:00 **OBSTRUCTIVE RESPIRATORY DISEASES**
William R. Fifer, Minneapolis
Moderator
Norman G. Hepper, Rochester
James P. Lillehei, Minneapolis
Frank M. MacDonald, Minneapolis

MONDAY AFTERNOON

P.M.

12:15 **ROUND TABLE LUNCHEONS**

1:30 Visit scientific and technical exhibits

2:00 **TREATMENT OF BURNS**
Carl A. Moyer, Houghton, Michigan

2:30 **PANEL ON THE DYING AND THE DEAD**
Harold W. Hermann, Minneapolis
Moderator
Bishop James P. Shannon, St. Paul
Chairman
Rev. Elmer Hjortland, Oak Park, Illinois
Rabbi Albert G. Minda, Minneapolis

3:30 Visit scientific and technical exhibits

4:00 **RESPIRATORY DISTRESS SYNDROME IN THE NEWBORN**
Mary Ellen Avery, Baltimore, Maryland
Martha B. Strickland, St. Paul
Discussant

TUESDAY MORNING, MAY 17, 1966

The program on Tuesday is acceptable for 4½ accredited hours by the American Academy of General Practice.

A.M. Visit scientific and technical exhibits

9:00 **ISOTOPES AS A DIAGNOSTIC TOOL**
Paul V. Harper, Chicago, Illinois

9:40 **DIAGNOSIS AND TREATMENT OF HYPERTHYROIDISM**
L. O. Underdahl, Rochester

10:15 Visit scientific and technical exhibits

11:00 **PREVENTION AND TREATMENT OF KNEE INJURIES IN THE ATHLETE**
Harvey O'Phelan, Minneapolis
Professor Lloyd Stein, University of Minnesota

TUESDAY AFTERNOON

P.M.

12:15 **ROUND TABLE LUNCHEONS**

1:30 Visit scientific and technical exhibits

2:00 **JUVENILE DIABETES**
Priscilla White, Boston, Massachusetts
Donnell D. Etzwiler, Minneapolis
Discussant

2:30 **THE NEWER CONCEPTS IN THE TREATMENT OF STAPH AND STREP INFECTIONS**
Donald R. Nichols, Rochester

3:00 Visit scientific and technical exhibits

3:30 **THE EARLY RECOGNITION AND PREVENTION OF BLINDNESS**
Robert Hugh Monahan, St. Paul

4:00 **THE OB-GYN SEMINAR**
"Endometriosis, the Conservative vs. the Radical Surgical Treatment"
Bruce F. P. Williams, Duluth
"*Early* Invasive Carcinoma of the Cervix"
John M. McKelvey, Minneapolis
Joseph H. Pratt, Jr., Rochester

TUESDAY EVENING

7:00 **ANNUAL BANQUET**
Reception
Presentations
Entertainment, Dancing and Late Evening Buffet

Round Table Luncheons

Saint Paul Hotel

MONDAY — 12:15 P.M.

Fluids in Infancy
Mary Ellen Avery, Baltimore, Maryland

The Spiritual Dimension of Suffering
Harold W. Hermann, Minneapolis
W. F. Widen, Minneapolis

The Use of Saline Solutions in the Treatment of Hemorrhagic and Traumatic Shock
Carl A. Moyer, Houghton, Michigan

Treatment of Leukemia
A. B. Hagedorn, Rochester

Management of Emphysema
William R. Fifer, Minneapolis

Computers in Preventive Medical Research
Morris F. Collen, Oakland, California

TUESDAY — 12:15 P.M.

Prevention and Treatment of Ankle Injuries
Professor Lloyd Stein, Minneapolis

Value and Use of the Tonometer
Robert Hugh Monahan, St. Paul

The Brittle Diabetic
Priscilla White, Boston, Massachusetts

Radioactive Isotopes in Clinical Practice
Paul V. Harper, Chicago, Illinois

Amniocentesis, A Diagnostic and Therapeutic Tool
Bruce F. P. Williams, Duluth

Therapeutic Abortion in General and in Rubella
John M. McKelvey, Minneapolis

Program Highlights

. . . Dr. James Z. Appel, President of the American Medical Association, will address the House of Delegates at their opening session on Sunday, May 15. He will also be the speaker at the New Members, County Officers and Delegates dinner on Sunday evening.

. . . Please reserve Wednesday, May 18, following the annual meeting for an all-day session on the latest developments in Medicine. Mr. Roy K. Marquardt, regional representative for Health Insurance, Department of Health, Education and Welfare, is being asked to report on the up-to-the-minute status of Medicare. Other officials directly concerned with the program will also participate.

. . . For golfers — The annual golf tournament will be held on Sunday, May 15, at the White Bear Yacht Club followed by a dinner at 7:00 p.m. to which all members of the Association and their wives are cordially invited.

. . . Special attention is called to the day-long session on Monday of the Minnesota Society of Clinical Pathologists which begins at 9:00 a.m. at the Minnesota Club and continues through 4:30 p.m. The program will include a symposium on "Evaluation of Thyroid Function," and beginning at 2:00 p.m. "Case Reports" with panelists.

. . . Advance registration card for the meeting and the card for hotel accommodations were sent to all members with the Association's March newsletter. Use of these cards will save you time and greatly facilitate your attendance at the meeting.

. . . All high school coaches in the Twin Cities and surrounding area have been invited to hear Dr. Harvey O'Phelan and Professor Lloyd Stein discuss "Prevention and Treatment of Knee Injuries in the Athlete," a highlight of the Tuesday morning scientific session.

. . . The Association's 4th duplicate bridge tournament will begin at 9:00 p.m. on Monday night at the Saint Paul Hotel. It is open to all bridge players, duplicate experience is not necessary.

Sustained circulatory, respirator
and cerebral stimulation for th

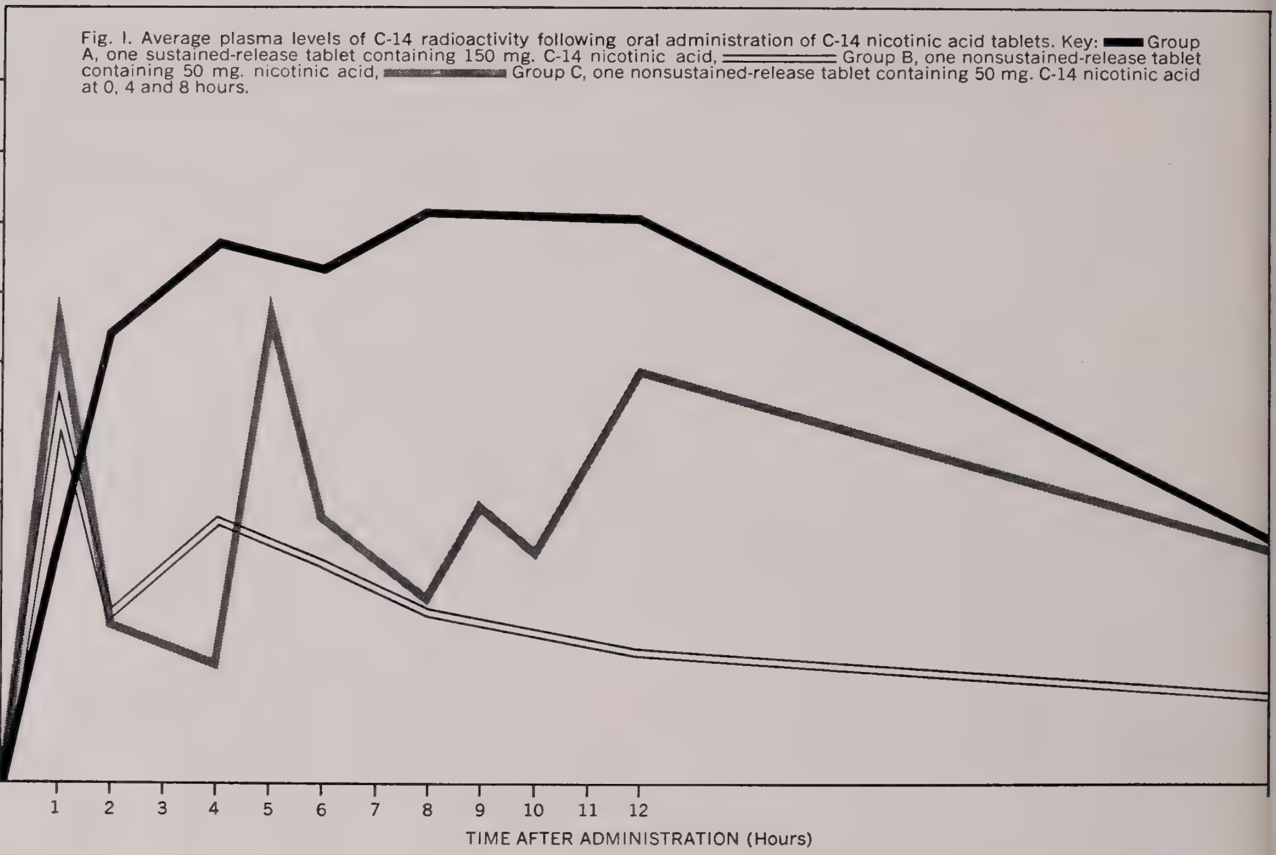

Fig. I. Average plasma levels of C-14 radioactivity following oral administration of C-14 nicotinic acid tablets. Key: ■ Group A, one sustained-release tablet containing 150 mg. C-14 nicotinic acid, ═ Group B, one nonsustained-release tablet containing 50 mg. nicotinic acid, ▨ Group C, one nonsustained-release tablet containing 50 mg. C-14 nicotinic acid at 0, 4 and 8 hours.

(fewer absent doses by absent-minded patients)

Human volunteer subjects were administered Geroniazol TT tablets with the nicotinic acid component made radioactive with C-14. Plasma and urine samples were analyzed. (See Figures I and II) The radioactive tracer study substantiated the previous clinical evidence that the release of nicotinic acid from the Geroniazol TT tablet produced a gradual rise in plasma levels to a plateau for a total of 12 hours and more.

Such proven sustained activity makes the management of geriatric patients much easier by minimizing the possibility of neglected doses through absent-mindedness or senile confusion. Therapy *can* be continuous on a daily dose of only one Geroniazol TT tablet every 12 hours.

The gradual release of nicotinic acid in Geroniazol TT will provide the well-known peripheral vasodilatation needed in patients with deficient circulation and with a minimum amount (if any) of "flushing." Also, cerebrovascular circulation is complemented by pentylenetetrazol, long-established as a cerebral and respiratory stimulant.

Geroniazol TT improves the typical, unfortunate, signs of senile confusion. Patients become more alert,

ged and debilitated

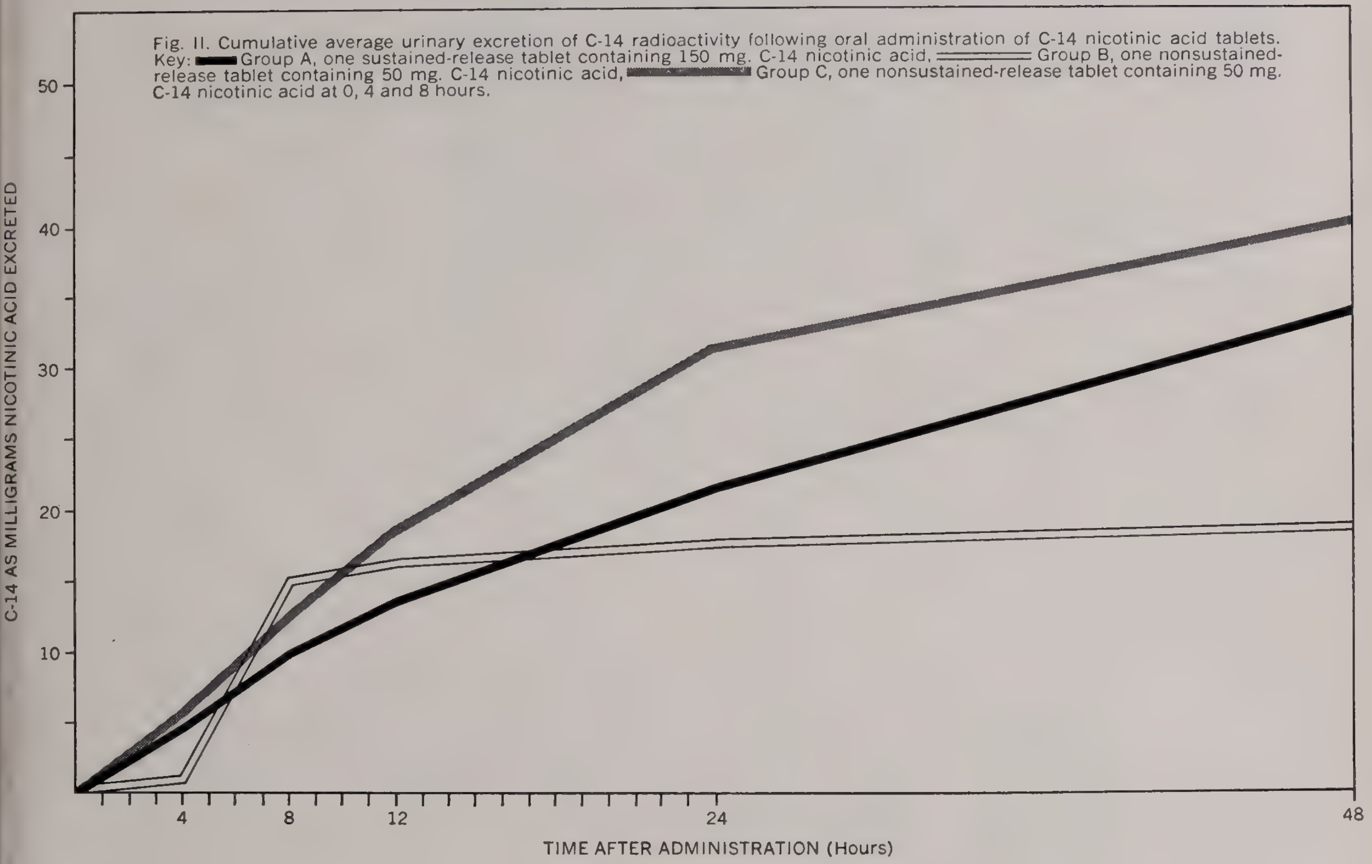
Fig. II. Cumulative average urinary excretion of C-14 radioactivity following oral administration of C-14 nicotinic acid tablets. Key: ━ Group A, one sustained-release tablet containing 150 mg. C-14 nicotinic acid, ═ Group B, one nonsustained-release tablet containing 50 mg. C-14 nicotinic acid, ▬ Group C, one nonsustained-release tablet containing 50 mg. C-14 nicotinic acid at 0, 4 and 8 hours.
C-14 AS MILLIGRAMS NICOTINIC ACID EXCRETED
50
40
30
20
10
4
8
12
24
48
TIME AFTER ADMINISTRATION (Hours)

less confused and moody. Personal care, memory, emotional stability, social attention improve. Fatigue, apathy and irritability are reduced.

A prescription for 100 tablets of Geroniazol TT will permit your patients to enjoy the benefits of time-prolonged nicotinic acid/pentylenetetrazol therapy, at an economical price. Dosage is only one tablet every 12 hours.

Contraindications: There are no known contraindications.

Precautions: Exercise caution when treating patients with a low convulsive threshold.

Side Effects: Side effects are rarely encountered, however due to the vasodilatation effect of nicotinic acid, transitory mild nausea, flushing, tingling and pruritus are possible.

Dosage: One tablet every 12 hours.

Supplied: Prescribe bottles of 100 tablets, to take advantage of recent price reduction.

References: 1. Report by Nuclear Science & Engineering Corp., Pittsburgh, Pa., in files of Philips Roxane Laboratories. 2. Connolly, R.: W. Virginia Med. J. *56*:263 (Aug.) 1960. 3. Curran, T. R., and Phelps, D. K.: Am. Pract. & Digest Treat. *11*:617 (July) 1960.

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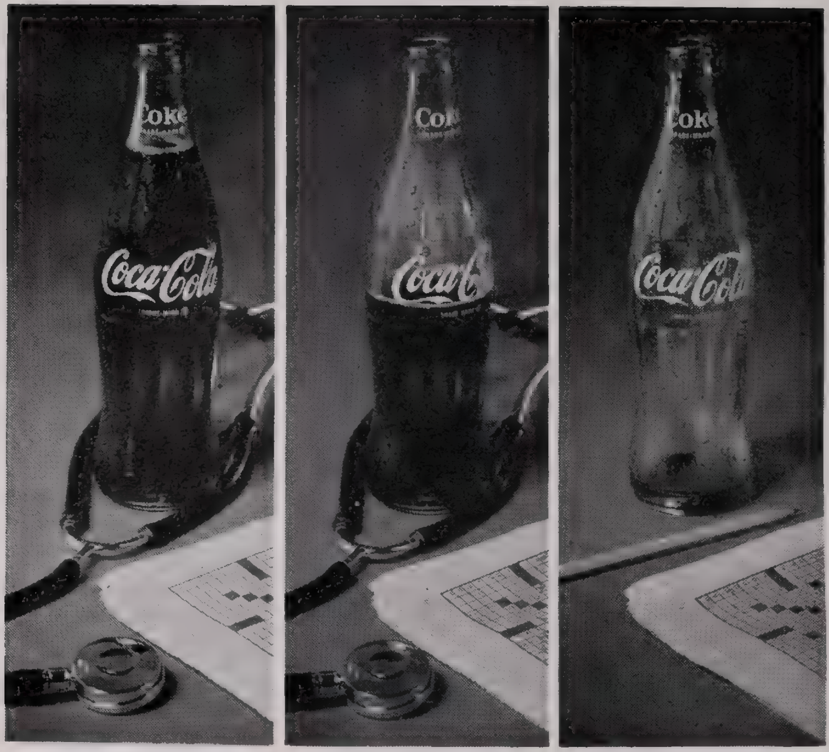

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Meetings and Announcements

Open your mouth and purse cautiously, and your stock of wealth and reputation shall, at least in repute, be great. — Zimmerman

APRIL

Minnesota Academy of General Practice meeting of House of Delegates, Hotel Radisson in Minneapolis, April 12, and annual refresher on April 13-14.

Minnesota Academy of Medicine meeting, Town & Country Club, St. Paul at 6:30 p.m., April 13.

St. Louis County Medical Society executive committee meeting, 6:00 p.m. regular meeting, 8:00 p.m., St. Luke's Hospital, Duluth, April 14.

Twin City Urological Society meeting, Town & Country Club, St. Paul, 6:00 p.m., April 15.

Ramsey County Medical Society meeting, 1500 Lowry Medical Arts Building, St. Paul, 8:00, April 25.

American Rehabilitation Foundation Nursing Course to be held at the Foundation, April 18 through May 6. Contact: Mrs. Jean Plass, R.N. at the Foundation, 1800 Chicago Avenue, Minneapolis.

Third Annual Midwest Conference on Anesthesiology sponsored by Illinois Society of Anesthesiologists in Chicago, Continental Plaza Hotel, April 28-30. Contact: T. L. Ashcraft, M.D., 33 East Cedar, Chicago.

American College of Physicians 47th Annual Meeting in New York City, April 18-22, Americana and New York Hilton Hotels. Contact: Edward Rosenow, Jr., M.D., 4200 Pine St.; Philadelphia, Pa.

MAY

Hennepin County Medical Society meeting, May 2 at 6:00 p.m., Pick-Nicollet Hotel, Minneapolis.

Hennepin County Psychiatric Society meeting to be held in connection with Hennepin County Medical Society Meeting on May 2.

Minnesota Society of Internal Medicine meeting, May 3 at 9:00 a.m. in Minneapolis.

Minnesota Academy of Medicine meeting, May 11 at 6:30 p.m., Town & Country Club in St. Paul.

St. Louis County Medical Society Executive Committee meeting, May 12, at 6:00 p.m., and the regular meeting at 8:00 p.m., St. Mary's Hospital in Duluth.

Minnesota Society of Clinical Pathologists meeting during Minnesota State Medical Meeting in St. Paul.

Minnesota Obstetrical & Gynecological Society meeting to be held in Rochester at the Mayo Clinic. The date to be announced.

Radiology and Pathology Departments of University of Wisconsin postgraduate course on radiology and pathology of urinary system, May 4-6, Wisconsin Center, Madison, Wisc. Contact: Thomas Meyer, M.D., 432 N. Lake St., Madison

ANNOUNCEMENTS

Dr. Birger Strandell, a member of the faculty of the Caroline Institute, Stockholm, and editor of ACTA MEDICA SCANDINAVICA, will lecture on "Linnaeus" at Rochester, May 10, 1966. The lecture, sponsored by the Mayo Foundation chapter of Sigma XI, will be held a day before the opening of the annual meeting of the American Association for the History of Medicine. Contact: Thomas E. Keys, 200 First Street Southwest, Rochester, Minnesota.

* * *

A symposium on Liver Disease will be held in the Mayo Auditorium of the University of Minnesota May 23, 24 and 25, in honor of Cecil James Watson, M.D. Symposium is open to all physicians at no charge.

* * *

Spring Cardiopulmonary Seminar will be held at Mount Sinai Hospital, May 19, 20. Contact: Jerome T. Grismer, M.D., Mt. Sinai Hospital, Minneapolis.

* * *

Minnesota State Medical Association Meeting, May 16-17, St. Paul Hotel, St. Paul. Contact: Harold W. Brunn, Executive Secretary, 496 Lowry Medical Arts Building, St. Paul.

* * *

Symposium on Functional Problems Confronting the Clinician in Everyday Practice, Friday, April 22, 1:00 p.m., St. Luke's Hospital, St. Paul. Contact: C. E. Turbak, M.D., St. Luke's Hospital.

* * *

One day educational program for physicians sponsored by Minnesota Heart Association, May 21, 8:30 a.m. at the Radisson Hotel in Minneapolis. Contact: Marie Nelson, 1821 University Avenue, St. Paul or Dr. Reuben Berman.

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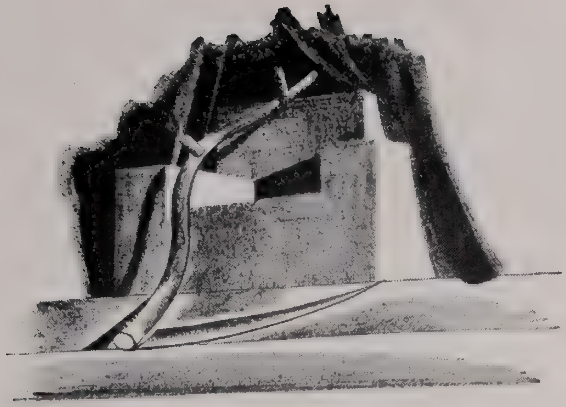

In Memoriam

The darkness of death is like the evening twilight; it makes all objects appear more lovely to the dying. — Richter.

HAROLD F. WAHLQUIST, M.D.

Dr. Harold F. Wahlquist, 72, Minneapolis physician, died February 5. He was a former chief of the medical staff at Methodist Hospital and charter member of the mayor's mental health board to organize a children's psychiatric clinic at General Hospital in 1958. He also was a former delegate to the World Health Organization and member of the Board of Directors of the Minneapolis Society for the Blind, Inc.

Dr. Wahlquist was born in Duluth, Minnesota and received his doctor's degree from the University of Minnesota Medical School. He was a member of the Hennepin County Medical Society, Minnesota State Medical Association and American Medical Association.

He is survived by his son and two daughters.

ALFRED L. LINDBERG, M.D.

Dr. A. L. Lindberg, 71, Wheaton physician, died February 10th in a Breckenridge hospital after a short illness. He was born in St. Peter, and upon earning his B.S. degree, taught in Long Prairie for a few years. This career was interrupted by his enlistment in the U. S. Army where he was inducted into the medical corps. Here he became interested in medicine and decided to enter the profession. He received his medical degree at the College of Medicine, University of Minnesota, in 1922, and after interning in Duluth, went to Wheaton in 1924. Dr. Lindberg practiced in Wheaton until 1961 when he retired from active practice.

He was a member of the West Central Minnesota Medical Society, Minnesota State Medical Association and the American Medical Association. His death came shortly before plans were completed by the people of Wheaton for a community-wide recognition program in his honor to be held in April.

He is survived by his wife.

OLIVER E. SARFF, M.D.

Dr. Oliver E. Sarff, 65, Duluth physician and urologist for many years, died January 16, following a long illness. Born in Milbank, South Dakota, he graduated from the University of Minnesota Medical School.

From 1961 to 1963 Dr. Sarff was surveyor for the Joint Commission of Accreditation of Hospitals. He was a member of the St. Louis County Medical Society, the American Medical Association, American College of Surgeons, American Board of Urology, American Urological Association and an associate member of the Minnesota State Medical Association.

He is survived by his son, Dr. Allen Sarff of Duluth, and a daughter.

MERRILL A. HOWARD, M.D.

Dr. Merrill A. Howard, 69, St. Paul physician, died March 1 in his home. He was born in Wells, Minnesota, and had lived in St. Paul for forty-four years.

Dr. Howard retired eight years ago from the practice of medicine because of ill health. He was a member of the American Legion Post 447, Ludwig Lodge 311, the American Medical Association, the Academy of General Practice, the Ramsey County Medical Society and an associate member of the Minnesota State Medical Association.

He is survived by his wife and two daughters.

EDWARD E. NOVAK, M.D.

Dr. Edward E. Novak, 92, a New Prague physician for seventy years and a well-known educator and livestock breeder, died March 7th. Born in Iowa, he received his medical degree from the University of Iowa in 1895. He began practice in New Prague the same year.

He was a University of Minnesota regent from 1937 to 1955 and was a former president of the Minnesota School Board Association. He had been a member of the New Prague School Board for forty years. Dr. Novak was a member of the Scott-Carver County Medical Society the American Medical Association. He was a life and 50 Club member of the Minnesota State Medical Association.

He is survived by his son and a daughter.

Classified

Classified advertising rates are twenty (20) cents a word; minimum monthly charge $5.00; key number, fifty (50) cents additional.

Replies to advertisements with key numbers should be mailed in care of MINNESOTA MEDICINE, *496 Lowry Medical Arts Bldg., St. Paul, Minn. 55102*

WANTED: General Practitioner who is interested in general practice and surgery to associate with a small group in West Central Wisconsin. Salary and partnership open. Write: MINNESOTA MEDICINE — 349, 496 Lowry Medical Arts Building, St. Paul 55102.

WANTED: Board eligible or certified general surgeon interested in one-year residency in colon and rectal surgery at the University of Minnesota Hospitals. Write to Chairman, Department of Surgery, University of Minnesota Hospitals, Minneapolis, 55455.

INTERNIST for 20-physician-clinic in prosperous Minnesota city. Salary negotiable first year, then full partnership. East Range Clinic, Virginia, Minnesota.

LOCUM TENENS wanted for general practice, six-man, Twin City group, from now through summer 1966. Write: MINNESOTA MEDICINE — 345, 496 Lowry Medical Arts Building, St. Paul 55102.

WANTED: young radiologist, board certified or eligible to join five man group consisting of four GP's and a general surgeon. University town of 6,000 in Northwestern Wisconsin close to Twin Cities. Salary open with early partnership. Write: MINNESOTA MEDICINE — 347, 496 Lowry Medical Arts Building, St. Paul 55102.

ANESTHESIOLOGIST needed to join me in midwestern private practice. Excellent financial arrangement. Send details in first letter. Write: MINNESOTA MEDICINE — 348, 496 Lowry Medical Arts Building, St. Paul 55102.

GENERAL PRACTITIONER to join active six-man, AAGP, two office group. Liberal vacation, rotating night call, life insurance. Metropolitan area, salary leading to partnership. Write: MINNESOTA MEDICINE — 346, 496 Lowry Medical Arts Building, St. Paul 55102.

PSYCHIATRIC RESIDENCIES positions available July 1, 1966 for a three year accredited program. A dynamically-oriented broadly-based well-balanced opportunity for sound training. Meadowbrook Hospital is Nassau County General Hospital and is centrally located in the most desirable and beautiful area in the country. Easy commuting distance to New York City. 2600 in-patient psychiatric admissions per year, 24 hour walk-in clinic, and all psychiatric modalities. Abraham S. Lenzner, M.D., Director Psychiatric Education, Meadowbrook Hospital, P.O. Box 175, East Meadow, New York 11554.

PART TIME INTERNIST OR GENERAL PRACTITIONER. Good compensation — Midway Area. Alfred F. Anderegg, M.D.; 2500 Como Avenue, St. Paul, Minnesota.

WANTED: Board Certified or eligible internist to associate with group in large, active practice in Minneapolis. Group consists of Surgeon, Obstetrician, Pediatrician and Internist maintaining downtown and suburban offices. Partnership in mind. Contact: Jesse J. Barron, M.D., 1127 Medical Arts Building, Minneapolis, Minnesota 55402, FEderal 2-8259.

BUSY, GROWING aggressive 3-man partnership in Northwest Wisconsin serving a trade area of 15,000 needs a well-trained recent graduate with fulfilled military obligations to associate immediately on excellent salary, with partnership in 1 year if mutually agreeable. Modern 15 room air conditioned brick clinic building is being doubled in size this year. 32 bed hospital and new 42 bed nursing home one minute from clinic. New 1500 student consolidated school. Excellent hunting, fishing and outdoor sport facilities in immediate area. Contact: MINNESOTA MEDICINE — 317; 496 Lowry Medical Arts Building, St. Paul 55102.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with early partnership. Write: MINNESOTA MEDICINE — 289; 496 Lowry Medical Arts Building; St. Paul, 55102.

WANTED: Generalist to associate with two man partnership in Northern Minnesota. Community has a thirty-seven bed hospital, X ray and laboratory technicians and nurse anesthetist. Good hunting and fishing. Adequate salary and time off. Contact: A. G. Janecky, M.D., Baudette Clinic, Baudette, Minnesota.

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WANTED — Internist, board certified or qualified, to associate with two board certified internists. Ten man multi-specialty group. (Lenont Peterson Clinic, Virginia, Minnesota) — Heart of the expanding taconite industry.

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WANTED: young general practitioner to join six-man group consisting of 4 GPs, a general surgeon, and radiologist. College town of 5,500, 30 miles from Twin Cities. Also need LOCUM TENENS in general practice. Contact: Ed Jenkins, Mgr., River Falls Medical Clinic, River Falls, Wisc. Phone 425-5322.

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GENERAL PRACTITIONER — MINNESOTA STATE PRISON. Serve as Medical Director of 50-bed hospital with staff of registered nurses and laboratory technician. Surgical resident provided by University of Minnesota. Consultant service in various specialties also available. Residence suitable for family, furnished free-of-charge. Minnesota Civil Service Position. Contact: Mrs. Barbara Sundquist, Box 55, Stillwater, Minnesota 55082 — Telephone 439-1910, Ext. 320.

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GENERAL PRACTITIONER — to join established five-man mixed group in progressive city of 15,000 in Southeastern Minnesota. Excellent clinic facilities situated adjacent to hospital. Annual vacation, post-graduate time, retirement and other benefits. Starting salary open with eventual equal salary and ownership. Contact: Richard F. Lehigh, Owatonna Clinic, 134 Southview, Owatonna, Minnesota.

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Continued to page 704.

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GENERAL PRACTITIONER to join general practitioner affiliated with group in neighboring town in northeastern Minnesota. Basically medicine and pediatrics on outpatient basis. Obstetrical and hospital practice optional. Eight days off each month in any mutually agreeable manner plus liberal vacation and study leave. No investment; full partnership after six months. Present doctor spends time in medical missionary work. Age no barrier. Contact Community Clinic, Two Harbors, Minnesota.

Physician's Diary

All men have their frailties; and whoever looks for a friend without imperfections, will never find what he seeks. We love ourselves notwithstanding our faults, and we ought to love our friends in like manner. — Cyrus

Dr. William H. Weidman, consultant in pediatrics in the Mayo Clinic, Rochester, was chosen president-elect of the Midwest Society for Pediatric Research at the organization's annual meeting in Chicago.

* * *

Dr. J. W. Duncan was honored recently for his thirty-five years in the practice of medicine in Moorhead by the Franciscan Sisters who operate the St. Ansgar Hospital.

* * *

Dr. Robert R. Kierland, head of the section of dermatology in the Mayo Clinic, was elected first president of the Dermatology Foundation, at the meeting of the board of trustees of the organization.

* * *

Dr. Merle S. Mark has been selected chief of the medical staff at Glenwood Hills Hospital in Minneapolis. **Dr. John W. Lawrow** was selected vice chief-of-staff and president-elect with **Dr. Walter Indeck** named secretary and treasurer.

* * *

Dr. Alton C. Olson, president of the Eitel Hospital medical staff, recently announced the officers of the Hospital. **Dr. Thomas M. Recht** was named chief-of-staff, and **Dr. Richard E. Anonsen**, assistant chief-of-staff, for a second term. **Dr. Marie Moorhead** was also named secretary-treasurer.

* * *

Dr. H. O. Morgan of Amboy has practiced medicine in that community for thirty years, and the entire town extended its congratulations to Dr. Morgan.

* * *

Dr. Fred A. Lyon of St. Louis Park will be installed as a fellow of the American College of Obstetricians and Gynecologists at its annual meeting in May in Chicago.

* * *

Dr. Ormond S. Culp, head of the Section of Urology in the Mayo Clinic, was elected president of the Clinical Society of Genito-Urinary Surgeons at its meeting recently, and **Dr. James T. Priestley**, head of a section of surgery at the Mayo Clinic, has been appointed a special consultant on the Clinical Research Training Committee of the National Institute of General Medical Sciences.

* * *

Dr. F. T. Becker is the newly named chief-of-staff of St. Mary's Hospital in Duluth. Other hospital staff members named were: **Dr. I. T. Clark**, chief of staff-elect, and **Dr. H. J. Meyer**, secretary.

* * *

Dr. David G. Smith of Watertown, **Dr. Theodore P. Myers** of Albert Lea and **Dr. Oliver Elwood Wiger** of Little Falls have been elected to active membership in the American Academy of General Practice.

* * *

Dr. Sumner Cohen has succeeded **Dr. Maxwell Barr** as president of the Mount Sinai Hospital staff in Minneapolis. Others elected to the medical staff include: **Dr. Jules Feinstein**, president-elect, and **Dr. Donald Fingerman**, secretary-treasurer.

* * *

Dr. Vincent Hunt of Red Lake Falls was elected president of the Red River Valley Medical Society at its mid-winter meeting, and **Dr. Cliff Stadem** of Fertile was elected vice president. **Dr. R. O. Sather** of Crookston was elected secretary.

* * *

Dr. Roger W. Brockway of Grand Rapids was installed president of the Range Medical Society at its annual meeting in January. **Dr. H. Wayne Johnston** of Virginia was installed as president-elect; **Dr. Kenneth A. Ahola** of Hibbing, vice-president and **Dr. Douglas J. Coy** of Grand Rapids, secretary-treasurer.

* * *

Dr. Robert V. Hodapp of Willmar, has been elected to a fellowship in the American Academy of Pediatrics at its recent annual meeting.

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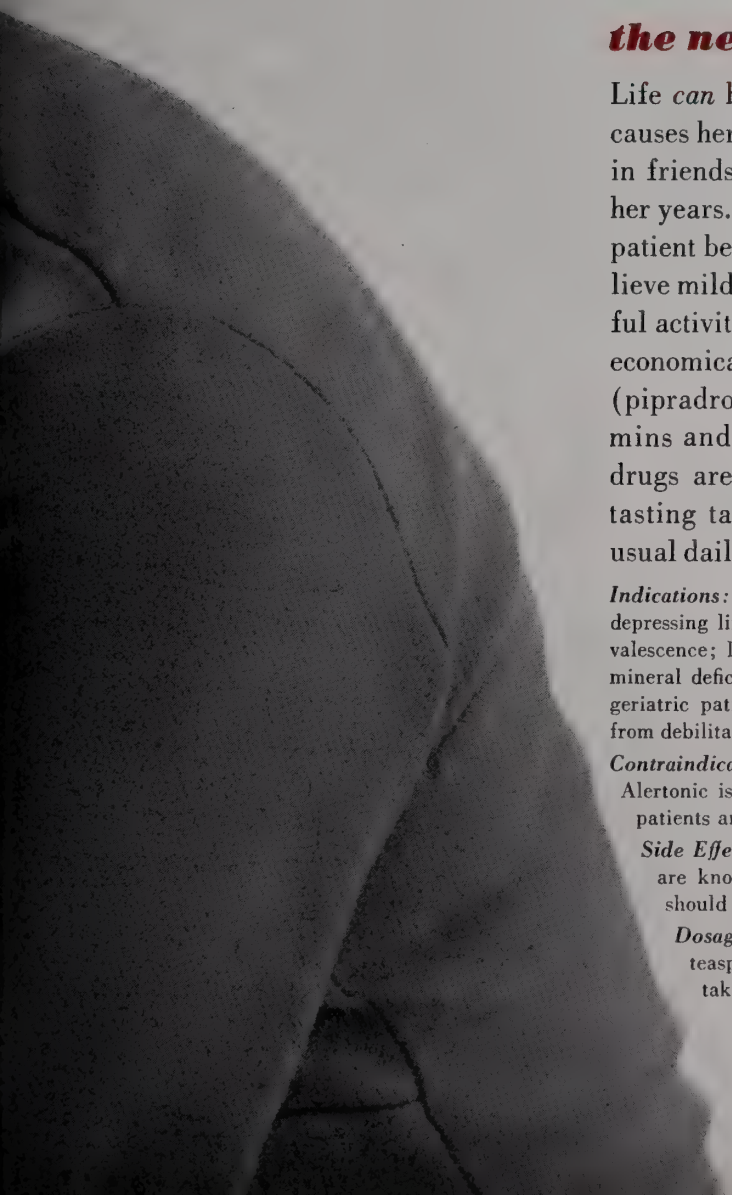

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Dosage: Adults, 1 tablespoonful; children (over 15 years old), 1 to 2 teaspoonfuls; children (4 to 15 years old), 1 teaspoonful. To be taken three times daily 30 minutes before meals.

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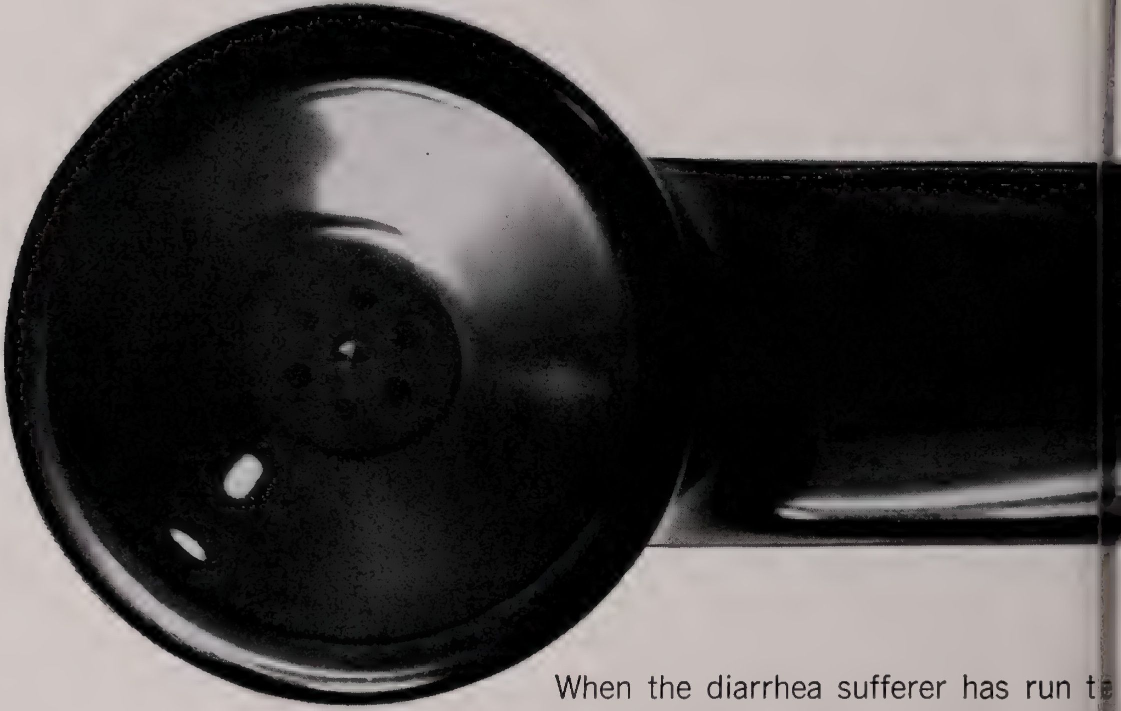

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Minnesota Medicine at a Glance

Hearing Problems — Hilger Page 561

For the doctor who must attend to a great variety of disease processes pertaining to the ears, Hilger has detailed many procedures and diagnostic methods which can be readily applied in the office of one who is equipped to deal with them. From a review of this manuscript one can no doubt improve his office handling of numerous ear problems.

Aortoiliac Occlusion — Monge′ and LaBree Page 566

Aortoiliac occlusion can usually be diagnosed clinically on the basis of claudication in the hip, thigh, or calf. There may be marked ischemia and a diminution or absence of pulsation at the femoral artery in the groin. Translumbar aortography or distal arteriograms confirm the diagnosis in a high percentage of cases, and this procedure is useful in aiding the surgeon in making an evaluation of the proper operative procedure in advance of the exploration.

A bypass prosthetic graft proved to be the most successful technique for relieving aortoiliac occlusion, and though the incidence of subsequent major sequellae is high, this procedure offers some hope for those who might otherwise suffer almost total disability.

Small Bowel Tumors — Scott and Grossling Page 572

Primary small bowel tumors occur so infrequently as to be unsuspected in many instances when a patient's symptom is that of anemia with an unexplained origin. It would be well to review this manuscript in order to recall to mind that the most common clinical feature is that of gastrointestinal bleeding, obstruction, abdominal pain, and a palpable mass.

X-ray examination is capable of providing diagnostic suspicion in approximately one third of the cases.

Lupus Erythematosus — Dubnow et al. Page 577

Abdominal pain may be a symptom of systemic lupus erythematosus. Rarely is this pain sudden and severe enough to simulate an acute surgical emergency. If leukopenia, anemia, and abnormal urinary constituents are present, systemic lupus erythematosus should be considered, and appropriate confirmatory studies made.

An interesting and pertinent article calling attention to an unusual facet of a not uncommon disease. The writer implies but does not substantiate that the proper treatment is intestinal resection.

Salmonella Pullorum Septicemia — ten Bensel and Williams Page 580

Salmonella organisms are known to be widely distributed in animals; but rarely do they infect man. Chickens infected with *Salmonella pullorum* are a constant concern to public-health authorities, as these asymptomatic birds may be producing eggs which are contaminated and which may subsequently infect man. Minnesota is fortunate in having a low incidence of infected birds; but from the case report of ten Bensel and Williams it is apparent that those few are a real and constant threat to man. Their patient apparently acquired *Salmonella pullorum* septicemia from eating raw eggs; certainly his underlying disease process rendered him more susceptible to this infection. Even though this is the first reported fatal case of *Salmonella pullorum* infection it is pointed out that the physician must take great care in the feeding of raw eggs, undercooked eggs or dried egg products until such time as these are known to be free of salmonellae.

Hepatolobectomy for Metastatic Neuroblastoma

— Brown and Hart Page 591

Partial hepatolobectomy has been performed more frequently in the past few years for benign lesions, and in a few instances total hepatolobectomy has been done. For a child with neuroblastoma a hepatolobectomy was successfully done, though in this instance considerable morbidity was encountered and the child finally died at the end of about a year. It is of interest to note that roentgen therapy was able to reduce the size of the mass in the liver from an inoperable lesion to one that could be removed.

Neoplasms of the Nasopharynx — Medical Seminar Page 635

This discussion of nasopharyngeal tumors indicates the complexities and difficulties in differential diagnosis. When more than one cranial nerve is involved, the diagnosis sometimes is more readily arrived at from a clinical consideration rather than by extensive diagnostic procedures. However, occasionally nasopharyngeal lesions will be overlooked because the clinical picture suggests a tumor of the jugular bulb rather than a nasopharyngeal malignancy. A careful nasopharyngeal examination is extremely important and should be recommended before intracranial exploration of the jugular bulb is attempted.

Alcoholics — Heart Disease — Grand Rounds Page 653

Heart disease has a variety of causes, and in most instances the etiologic factors, which include coronary artery disease, hypertension, and various toxic and infectious processes, become evident after a short period of evaluation.

The more unusual causes for heart disease, which are not as readily evident, may be accurately diagnosed if one keeps in mind that heart disease can result from malnutrition leading to thiamine deficiency, and can also be accounted for in a similar manner in a chronic alcoholic. The case reports detailed in the Grand Rounds are worth a total review.

Manifestations of Cancer — Nuessle Page 659

The systemic manifestations of malignant neoplasms are presented in considerable detail. Awareness of these manifestations, such as thrombophlebitis, hypoglycemia, hypercalcemia, hyperuricemia, erythrocythemia et cetera, along with the knowledge that such entities as dermatomyositis, acanthosis nigricans, Peutz-Jegher's syndrome and herpes zoster, may indicate an underlying malignant neoplasm and will help the clinician in earlier detection of cancer.

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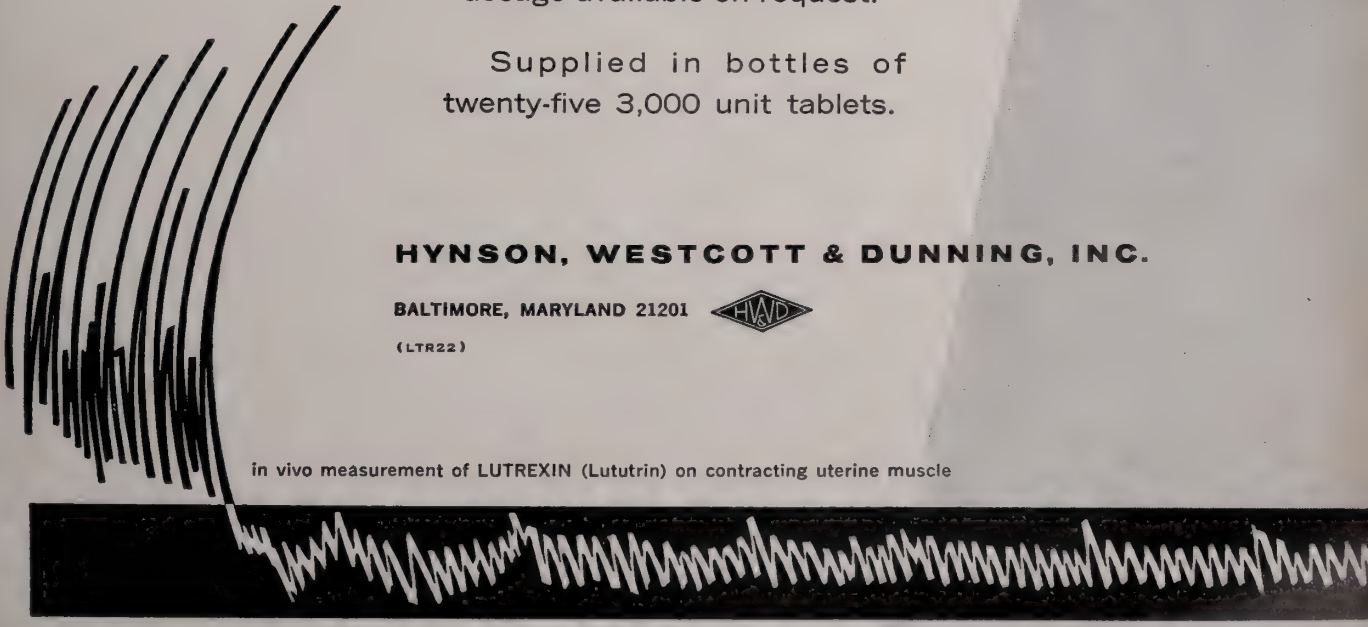

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Volume 49

Number 5

PRESIDENT'S LETTER 723

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University of Minnesota

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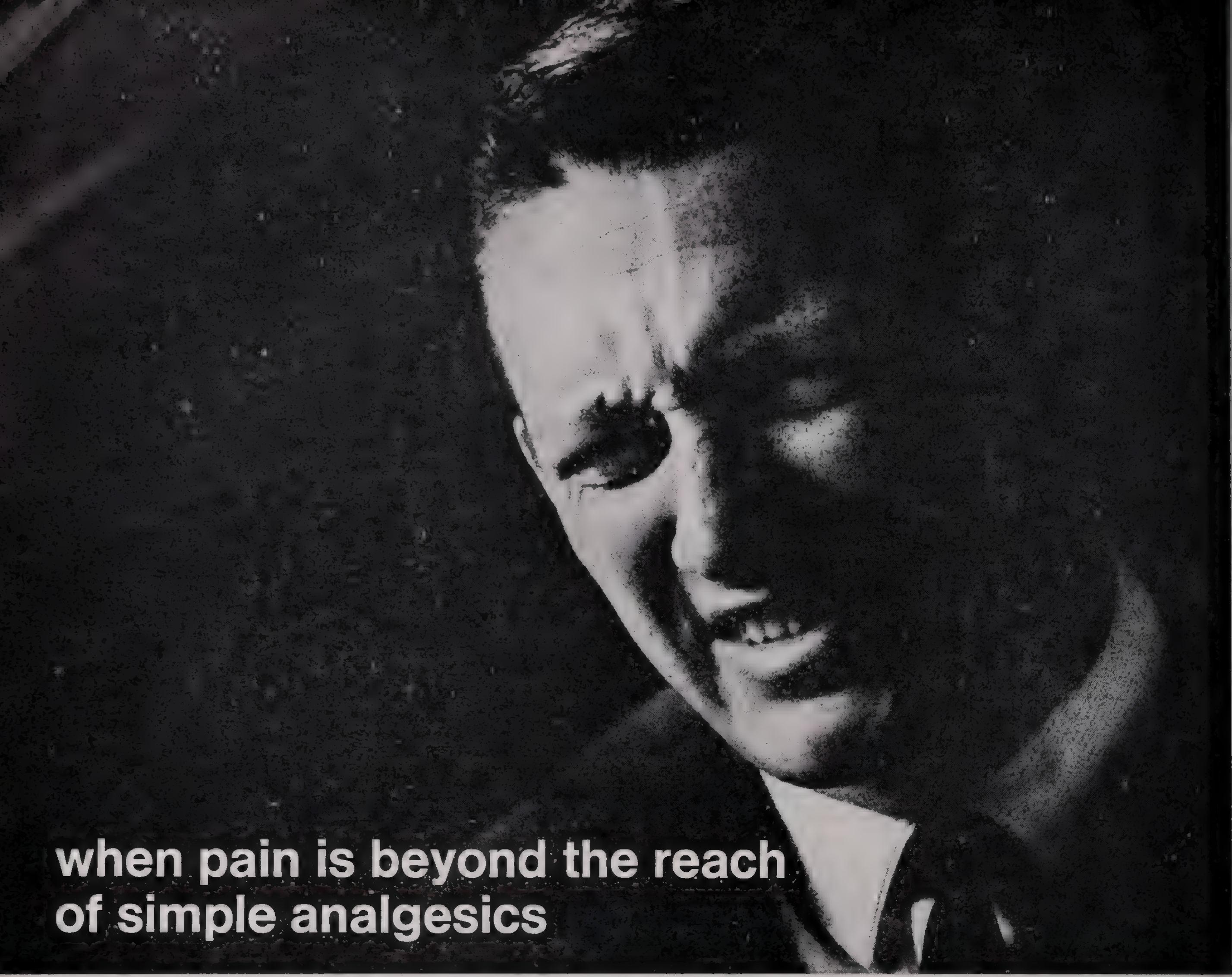
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President's Letter

Recently the American Medical Association, through the Council on Drugs, announced the development of a Registry on Adverse Reactions. The announcement is also an appeal to individual physicians to report, on forms, supplied on request directed to the Registry, all adverse reactions to any therapy observed in individual patients.

Cooperation by physicians is to physician advantage; for by the sheer weight of individual reports, otherwise unidentified reactions will be recorded, classified, and taped as a living, growing compilation, to identify the rare cases and report any suggestive trends in unexpected results, as well as the frequency of those results.

No problems exist in the area of confidentiality, for all reporting physicians are identified simply by code, and only with a physician's consent will his name be revealed in the event further educational study is indicated.

The patient in turn will be identified only by initial, date of birth, sex and race; and in any scientific exchange program the identity of the patient, the physician and the hospital remains confidential.

Legal opinion supports the position that no risk is involved in reporting adverse reactions. No liability for negligence can be incurred by either physician, hospital or other reporting group.

Recalling that hospitalized patients who have unexpected results from any therapeutic measures have, in those hospitals where adequate clinical records are kept, a fully recorded description of such unexpected results, a registry is in actuality only an extension of such a record. The implications in this American Medical Association endeavor are obvious.

Since the program is essentially an educational one, conclusions, warnings and suggestions will be made available to physicians through professional media. In addition, individual problems will be considered and individual assistance provided by panels of outstanding consultants, on a personal basis to those physicians requesting information and advice from the registry.

This request, an invitation to participate in a purely medical program of distinct benefit to patient and physician alike, refreshingly free of any of the political implications so prominent in recent and continuing medical activity, deserves the cooperation and interested participation of every physician.

This issue of MINNESOTA MEDICINE is dedicated to Dr. Gerald T. Evans, Professor and Head of the Department of Laboratory Medicine of the University of Minnesota. Dr. Evan's brilliant and productive career in Clinical Laboratory Medicine, his many contributions, his untiring efforts to produce quality-controlled laboratory procedures should be an example for each of us to make our individual contribution, as requested by the Registry, to this lesser but significant area of progress in medicine.

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Immunogenesis, Leukemogenesis and Experimental Auto-Immunity

ROBERT A. GOOD, Ph.D., M.D.[*]
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MAX D. COOPER, M.D.[†]
RAYMOND D. A. PETERSON, M.D.[‡]
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Minneapolis, Minnesota

OUR VIEW OF the lymphoid system of tissues and cells has undergone rapid revision during the last few years and is still in a period of redefinition. Any current concept is necessarily a partial one and subject to modification as new clinical and experimental evidence becomes available. There are two basic divisions we should like to consider. The first distinction we see is that of *central* versus *peripheral* lymphoid tissue. The prototype of a central lymphoid tissue is the thymus, an organ originating in the epithelium of the gut, a "source" tissue in the ontogenesis of most of the rest of the lymphoid system, and an important factor in immunogenesis, lymphoreticular malignancy, and "auto-immunity." The bursa of Fabricius of the chicken and the appendix of the rabbit are also in this category; other tissues of this type undoubtedly exist, particularly in higher mammals. The prototype of a peripheral lymphoid tissue is the spleen (and in mammals, the lymph nodes), dependent on central lymphoid tissue in late embryonic and early postnatal life, but relatively autonomous in the mature organism.

The second division is one which has been implicit in a number of clinical observations during the last year or two, but which has only recently been demonstrated in an experimental model in the chicken. The data suggest that there are two lymphoid systems in a sense, one dependent on the thymus and thymus-like central lymphoid tissue, and the other dependent on the bursa (in chickens) and bursa-like central lymphoid tissue or tissues in mammals. The cell type typical of the thymus-dependent lymphoid development is the small lymphocyte; the cell type

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From the Pediatric Research Laboratories of the Variety Club Heart Hospital, University of Minnesota, Minneapolis.

Aided by grants from the National Foundation, American Cancer Society, U. S. Public Health Service (HE-02085, NB-02042 and AI-00798) and American Heart Association.

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typical of the bursa-dependent lymphoid development is the plasma cell. Functionally, the thymus-dependent system seems to represent immunologic recognition. In responses of the delayed hypersensitivity type it is apparently also the effector system; in responses of the circulating antibody type it apparently passes "information" to the other system which actually produces the immunoglobulins.*

Types of Immunologic Deficiency

On this basis, we can classify two types of immunologic deficiency and two types of lymphocytic malignancy, depending on the system of cells involved.

Thymus-Based Immunologic Deficit

The immunologic depression produced in mice, rabbits, rats, and hamsters by neonatal thymectomy (or, in the case of rabbits, by thymectomy and/or appendectomy) has affected recognition; these animals may have extremely deficient reactions of delayed hypersensitivity and transplantation immunity, but have normal numbers of plasma cells and normal levels of immunoglobulins. In the chicken a similar model is produced by thymectomy and sublethal irradiation in the immediate post-hatching period. All of them are deficient in specific antibody production, however, because the recognition system is awry. Consistent with this view is the finding that neonatally thymectomized mice and rabbits often have Coombs-positive red blood cells and organic lesions of the "auto-immune" type.

Agammaglobulinemia

The second type of immunologic defect is that found in the sex-linked recessive type of agammaglobulinemia in humans and also in chickens subjected to bursectomy and sublethal irradiation in the immediate post-hatching period. Neither these patients nor these chickens produce detectable antibody on repeated stimulation; however, there is every evidence that they recognize "foreignness" and are able to express cellular immunity. The experimental model of agammaglobulinemia is still being defined. We recently reviewed in some detail the pathogenesis of immunologic deficiency diseases in the context of the recent experimental work on the two systems.[21]

Reevaluation of Lymphoid Malignancies

Redefinition of both experimental and clinical lymphoid malignancies is indicated.

Bursa and Thymus-Dependent Experimental Lymphoma

The typical thymic lymphoma of mice is an ideal example of a thymus-dependent neoplasm; visceral lymphomatosis in the chicken is an ideal example of a bursa-dependent lymphoma. Removal of the appropriate tissue early in life almost completely prevents the occurrence of these malignancies.[12,15]

Clinical Lymphomas

Our knowledge of the range of immunologic deficiency in Hodgkin's disease[22] suggests that thymus or at least thymus-system involvement is basic in this disease, the thesis advanced in England some years ago by Thomson[23] on pathologic grounds. Giant follicular lymphoblastoma is the human disease most remindful of the follicular enlargement observed in chickens with visceral lymphomatosis, and it is of great interest that several patients developing acquired agammaglobulinemia have had a benign form of lymphoid hyperplasia of this type concurrently.

Some acute and chronic lymphatic leukemias seem to represent even in their initial stages involvement of the small lymphoid cells, those of the thymus-dependent system; plasma cell myeloma, of course, involves primarily the immunoglobulin system. We believe that the initial involvement in lymphoid malignancies is in only one of the cell systems, and that the immunologic status of the experimental animal or patient is sometimes indicative of the component involved very early in the disease. Much more work is needed on this problem even to suggest what the implications of this division are for diagnosis and treatment in human disease.

---

*The bibliography (references 1-20) lists two books, several reviews, and a number of basic individual research reports on the recent thymus-bursa work and its historical background.

Discussion

In ontogenetic development (and in cases of extreme lymphoid tissue depletion later in life) it seems probable that both of these tissues function both as a source of cells and of humoral substances which foster lymphoid cell development and maturation of immunologic competence.[17,24-27] The essential defect is at the peripheral level, however, and it seems, at least in the case of the mouse thymus, that the stroma is not essential if a sufficient number of histocompatible lymphoid cells can be provided the neonatally thymectomized animal by intraperitoneal injection.

Auto-Immunity

Woven through much of the current literature and discussion of the thymus is the concept of auto-immunity: that thymic abnormalities are associated with clinical and experimental syndromes characterized by serologic and pathologic manifestations often grouped as "auto-immune" phenomena. Thus, germinal center development and plasma cells have been observed in the thymuses of patients with myasthenia gravis, lupus erythematosus, and thyrotoxicosis, in which one or more auto-antibodies are usually found in the circulation. Similar lesions have been observed in the NZB/BL mice, an inbred strain with a very high incidence of Coombs-positive anemia.[28] Coombs positivity is also seen in some strains of neonatally thymectomized mice[29] and in rabbits subjected to neonatal thymectomy or appendectomy-thymectomy.[30] Neonatally thymectomized mice, observed by deVries and his colleagues[29] in Holland, have had LE-like lesions of the heart and kidney as well as abnormal antibodies. We have been especially attracted to the relation of auto-immunity to immunologic deficiency in view of our own experience and that of other clinical groups that agammaglobulinemic patients have an unusually high incidence of "auto-immune" diseases; since they form virtually no antibody of any kind, these patients have the disease without the customary auto-antibodies. The most obvious unifying concept, of course, is that we are dealing with virus or mycoplasma infections, and that any form of immunologic deficiency is likely to favor the development of clinical disease. Blunted immunologic recognition might also favor abnormal antibody formation to self-constituents in damaged tissues, a development which might in turn result in further tissue destruction.

Addendum

In preliminary experiments, humoral immunity has been selectively depressed in rabbits by removal of the appendix, sacculus rotundus, and Peyer's patches. This has been done by removing the tissue in newborn animals, and by removing the tissue at a later age and irradiating the rabbits. Cellular immunity remains intact in both instances.

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8-30 May be secured from the author or the reprints.

The Penalty of Overweight

There is widespread agreement that mortality and morbidity from cancer are increased in the presence of obesity.

— Cyril M. MacBryde, M.D., Signs & Symptoms, Lippincott Co.

Human Serum

In 1950 Gould and Taylor reported a marked suppression of newly synthesized cholesterol in the liver and plasma of dogs ingesting a high cholesterol diet[1] (Figure 1), and others demonstrated a similar homeostatic mechanism in rats.[2] The mechanism of this inhibition of cholesterol synthesis by dietary cholesterol has been studied extensively and shown to possess the characteristics of a negative "feed-back" mechanism or control system. Thus, in this control system, a single reaction, the reduction of Beta-OH Beta methyl glutaryl CO A to mevalonic acid, was shown to be the primary site of depression of cholesterologenesis produced by exogenous (dietary) cholesterol.[3] Studies in our laboratories have shown an almost complete lack of change in the rate of appearance of newly synthesized plasma cholesterol in man regardless of the type of diet employed (cholesterol-rich or cholesterol-low)[4] (Figure 2). These findings corroborated earlier studies which indicated that man (unlike the dog and rat) has little demonstrable "feed-back" control of in vitro hepatic cholesterol synthesis.[5]

Employing an indirect method for estimating relative contributions of dietary and endogenously synthesized cholesterol to plasma cholesterol (reported by Morris and others in studies on rats[6]), we fed ring-labeled 4-C^{14} cholesterol to dogs and humans.[7,8] Our studies in the dog were comparable to those reported in the rat by Morris and others; both animals demonstrated nearly complete replacement of endogenous sources of plasma cholesterol by ring-labeled dietary cholesterol (Figure 3). The indirect studies were in good agreement with earlier studies demonstrating the dominant homeostatic role played by the liver in the cholesterol metabolism of the rat and the dog. The

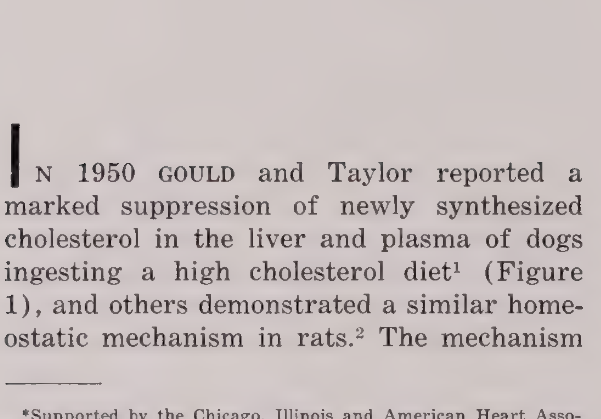

Fig. 1 — Effect of dietary cholesterol on in vitro cholesterol synthesis by liver slices in dogs. Estimated mg. of cholesterol synthesis per 100 gm. liver are plotted on the ordinate; hours incubated in presence of C^{14} acetate are plotted on the abscissa. Control dogs were on cholesterol-free diets before liver biopsies were taken for incubation. Cholesterol-fed dogs were fed 1 gm. cholesterol in oil 12 hours before liver biopsies were taken for incubation. Estimations of cholesterol synthesis were determined from quantities of C^{14} acetate incorporated into cholesterol molecules isolated from incubated liver slices.

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Cholesterol Synthesis*

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results from the ring-labeled cholesterol feeding studies in man were very different from those observed in dogs and rats. Only about a quarter to a third of labeled dietary cholesterol appeared in plasma with the remaining large fraction of ¾ to ⅔ of plasma cholesterol apparently being derived from endogenous synthesis (Figure 4). Since most subjects showed a rise in serum cholesterol while on the ring-labeled cholesterol regimen, there is suggestive evidence that, in the human, dietary cholesterol is added to an essentially quantitatively unaltered endogenous supply of plasma cholesterol.[8]

To better understand cholesterol metabolism in man and to determine the effects of dietary cholesterol on the rate of synthesis of serum cholesterol a deuterium labeling technique was employed. The rationale and methods were based on the work of London and Rittenberg (1950), who showed that a single adult male subject on a regular diet (probably containing 0.5 to 1 gm. of cholesterol per day) had about 0.5 gm. of newly synthesized cholesterol appear in his plasma each day.[9] Since much of the quantitative estimation of human cholesterol synthesis is based on this study, we felt the need for similar studies with subjects on cholesterol-free and cholesterol-rich diets.

Methodology

Eight endogenous serum cholesterol synthesis studies were carried out on five healthy human subjects (male and female). The subjects' age, race, sex and national origin varied considerably. Each subject served as his or her own control and they were alternately placed on a cholesterol-low diet and cholesterol-rich diet. The cholesterol-low diet consisted mainly of egg whites, beans, lentils, powdered fat-free milk and dry cottage

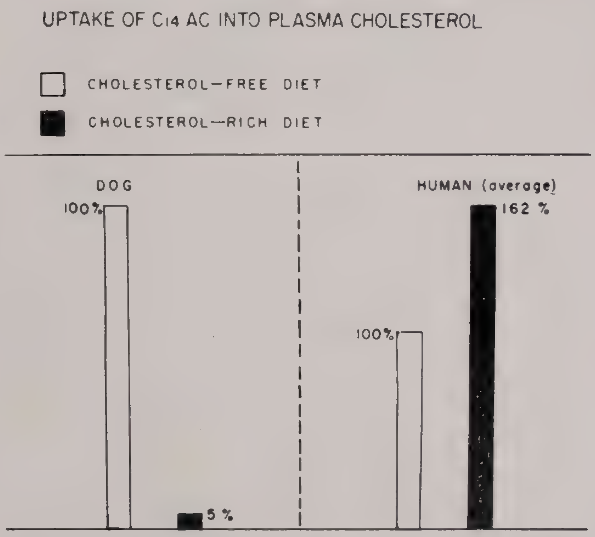

Fig. 2 — Effect of dietary cholesterol on appearance of C^{14} acetate-labeled endogenously synthesized cholesterol in plasma of dogs (on left) and man (on right). Clear bars represent amounts appearing when dog and eight subjects were on cholesterol-free diets; dark bars represent relative quantities appearing while dog and subjects were on cholesterol-rich diets. The 100% for cholesterol-free values was arbitrarily chosen as base line for this graph. Dog shows marked suppression (to 5%) of rate of appearance of labeled plasma cholesterol, whereas human subjects showed no compensatory suppression. Value of 162% for human subjects was probably over 100% because of shift in pathways for use of acetate pool caused by feeding of neutral fat with cholesterol.

cheese. This regimen excluded meat, egg yolks, cream, butter fat. All subjects were placed on this diet six weeks prior to the initiation of the studies.

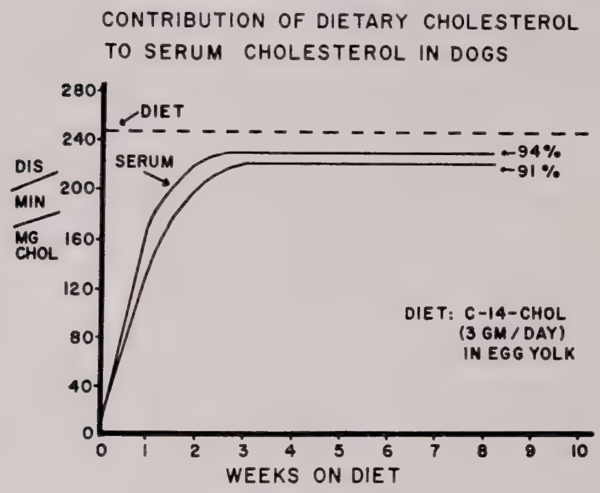

Fig. 3 — Graph presenting appearance of ring-labeled (4-C^{14}) dietary cholesterol in serum cholesterol of dogs. Radioactivity in disintegrations per min./mg. cholesterol is plotted on abscissa; time in weeks, on ordinate. Dotted line across top plots dietary radioactivity. Note that within three weeks the two dogs showed that 91 and 94% of their serum cholesterol contained the ring label, indicating that these percentages of serum cholesterol were derived from diet.

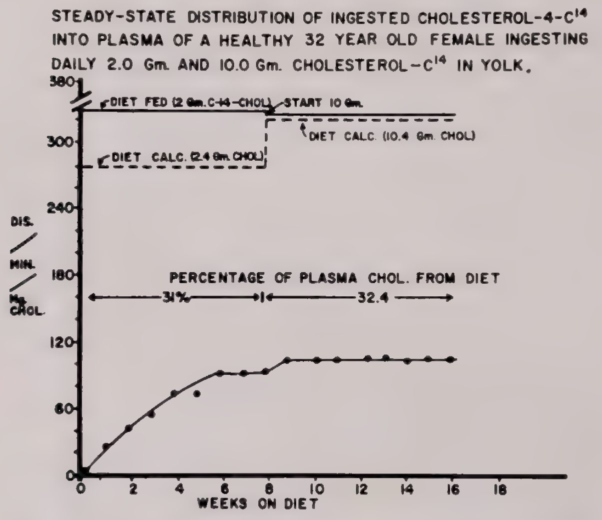

Fig. 4 — Graph similar to that of Figure 3, presenting rate of appearance of labeled (4-C^{14}) dietary cholesterol in serum of 32-year-old female subject. At about six weeks only 31% of serum cholesterol was derived from labeled dietary cholesterol. Interestingly, changing the diet from 2 gm. cholesterol/day to 10 gm./day resulted in only a minimal rise (to 32.4%) in per cent of serum cholesterol derived from labeled dietary cholesterol.

Baseline levels of normally occurring deuterium in urine and in serum cholesterol were obtained from all subjects. Subsequently, subjects were administered an oral priming dose of heavy water (D_2O) in concentrations high enough to raise the body water D_2O content to 0.5 moles % in excess of normal baseline D_2O. Doses averaged from 140 to 250 gm. D_2O. Thereafter, subjects received oral doses of D_2O daily, approximating 10% of their original priming dose to compensate for normal turnover of body water. All studies were run for a period of at least 40 to 50 days, and almost daily urine and serum samples were collected.

After completion of this initial study, subjects were allowed 7-10 months for the elimination of D_2O of body water, cholesterol and other endogenously synthesized deuterated organic molecules. Mass spectrometric analysis verified the return to baseline levels of the D_2O contents of body water and serum cholesterol.

The cholesterol-rich study was then instituted. This study provided an estimated daily dietary intake of 2.5 to 3.0 gm. cholesterol. The egg was the major cholesterol-carrying vehicle since an egg yolk contains approximately 250 mg. cholesterol. Again, urine and serum samples were collected almost daily for determination of deuterated body water levels and deuterium concentration in newly synthesized cholesterol.

The isolation, combustion and reduction of serum cholesterol were carried out in the following manner. Serum specimens were hydrolyzed with alcoholic KOH and extracted with petroleum ether and one portion of the extract analyzed for total serum cholesterol by the Abell-Kendall procedure[10] using a Lieberman color reaction (20-1, acetic anhydride-sulfuric acid). The remainder was converted to cholesterol digitonide. Pyridine was then added in order to split off the digitonide, and the cholesterol was extracted with acidified ether, purified and weighed. Specimens so isolated usually yielded from 2 to 4 mg. of pure cholesterol.

The isolated cholesterol was then combusted with copper oxide at 600°C. under high vacuum conditions in a sealed ampule of

Corning #1720 ignition glass. The ampule containing the CO_2 and H_2O of combustion was then placed in liquid nitrogen in order to condense and freeze the gases formed. Carbon dioxide was removed, and water driven over into a reduction ampule containing 0.5 gm. zinc. The reduction tube was then heated to 500° C. in order to reduce the H_2O and D_2O to H_2 and D_2 gas.

The deuterium assays were carried out in a Nier Model, RCA isotope ratio mass spectrometer at the Mayo Clinic. The mass spectrometer analyses consisted of measuring the mass 3 to mass 2 ratio. This ratio was then converted to heavy water concentration by reference to a calibration derived from five standards of various concentrations of D_2O and H_2O. The magnitude of error in the reduction and mass spectrometer analyses was of the order of ±4%.

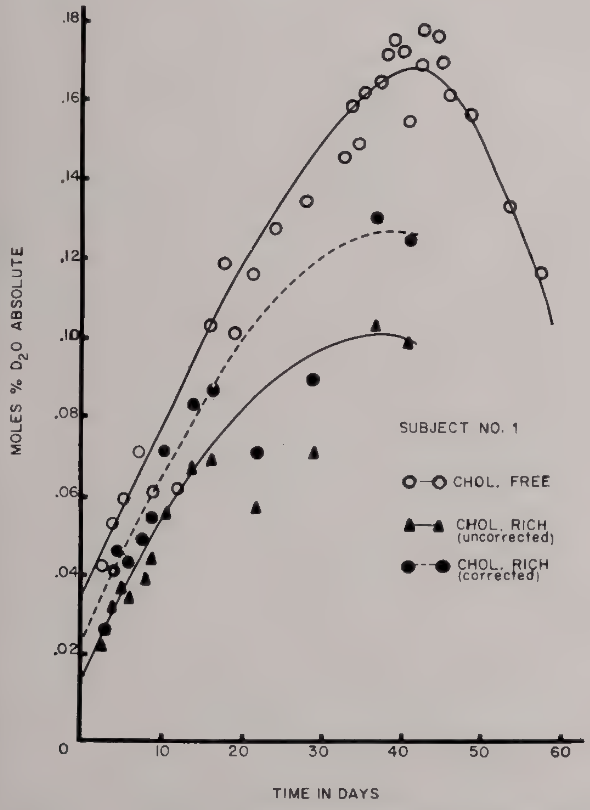

Fig. 5 — Serum cholesterol-deuterium enrichment curves of Subject 1 while on cholesterol-free (○——○) and cholesterol-rich diets (▲——▲). The middle curve is derived from corrected data of cholesterol-rich curve to correct for dilution of deutero-cholesterol by unlabeled dietary cholesterol. (See text for discussion of this correction.) Note again lack of effect of dietary cholesterol on rate of appearance of endogenously synthesized, labeled cholesterol.

Results and Discussion

The principal advantage of using deuterium is its negligible radioactivity which makes it possible to carry out long-term studies on humans without radiation as a hazard.

By enriching each subject's body water deuterium with the initial priming dose and daily doses of deuterium oxide, we were able to elevate and maintain the subject's labeled body water between 0.5 and 0.6 moles % D_2O. The labeling of newly synthesized cholesterol was adequate to provide meaningful data when D_2O enrichment was at 0.5 moles % D_2O in body water. Maximum enrichment of 0.1% D_2O in body water was shown to be experimentally unsatisfactory.

The maximal deutero-cholesterol concentrations were reached by 38-44 days in all eight studies. (Figure 5 is a graph of data from two studies on one subject.) These times are comparable to the study reported by London and Rittenberg in which maximum deutero-cholesterol-digitonide concentrations were reached on the 36th day.

Exogenous cholesterol feeding markedly

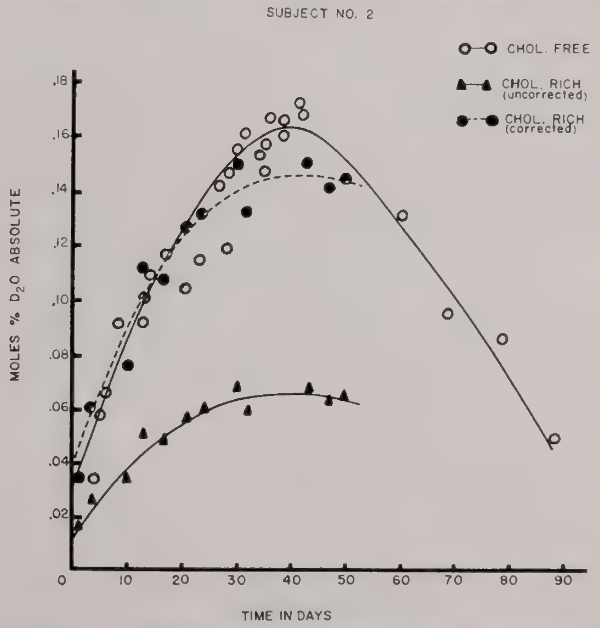

Fig. 6 — Serum cholesterol-deuterium enrichment curves of Subject 2. As discussed in the text, this subject's serum cholesterol increased 56% while he was on the cholesterol-rich study, resulting in a decreased maximum deuterium enrichment from over .16 to about .06. When corrections for exogenous dilution were made, the lower (cholesterol-rich) curve became very similar to the cholesterol-free curve.

increased the serum cholesterol levels. There was a marked increase in serum cholesterol of from 20 to 56 per cent. Since our studies showed simultaneous marked reduction of absolute deutero-cholesterol concentrations in the cholesterol-rich subjects, we felt this lower specific activity was due to the dilution effect of exogenous cholesterol on endogenously synthesized deutero-cholesterol. The most striking example was Subject 2 (Figure 6), whose mean serum cholesterol increased 56% while on the cholesterol-rich diet. His absolute deutero-cholesterol concentration, however, fell from 0.1640 moles % (cholesterol-low diet) to 0.0650 moles % D_2O on the cholesterol-rich diet. We corrected for the dilution of endogenously synthesized deutero-cholesterol by dietary cholesterol by determining the degree of dilution by exogenous cholesterol and increasing the moles % D_2O absolute by a corresponding factor. The effectiveness of this correction is demonstrated by the corrected curve obtained when the subject was on the cholesterol-rich diet. This effect was seen in all corrected curves.

By plotting the data on semi-log paper (in the manner of London and Rittenberg) one can obtain the half-life of serum cholesterol. This half-life is the time required to reach 50% of maximum deutero-cholesterol concentration. It also represents the time required for half the serum cholesterol molecules present in circulation to be synthesized. After one obtains the t ½, he can calculate the turnover rate of plasma endogenously synthesized cholesterol. This turnover is the mean survival time of serum cholesterol

TABLE 1

This table tabulates t 1/2 and $\bar{T}$ values for subject studied by London and Rittenberg and four of our subjects. Three subjects were studied while on both a cholesterol-free and a cholesterol-rich diet. Dietary effects on these values were negligible. A fifth subject receiving a much lower labeling dose of D_2O is not listed.

Col. I Subject	Col. II Diet	Col. III t 1/2	Col. IV $\bar{T}$
Subject of London & Rittenberg	? Chol.-Rich	8	12
No. 1	Chol.-Free	10.5	15.0
No. 1	Chol.-Rich	10.0	14.4
No. 2	Chol.-Free	8.0	11.6
No. 2	Chol.-Rich	8.5	12.3
No. 3	Chol.-Free	12.5	18.0
No. 3	Chol.-Rich	12.0	17.3
No. 4	Chol.-Free	9.5	13.7

TABLE 2

This table tabulates data used for estimation of gm. of plasma cholesterol synthesized per day. You will note that in subjects 1, 2 and 3 the total plasma cholesterol in gm. during cholesterol-rich studies has been corrected for estimated dilution by unlabeled dietary cholesterol. Estimated gm. of plasma cholesterol synthesis/day of London and Rittenberg and of our subjects are listed in the right-hand column.

Col. I Subject	Col. II Diet	Col. III $\bar{T}$	Col. IV Plasma Volume	Col. V Mean Serum Choles-terol mg. %	Col. VI M = Total Plasma Chol. gm.	Col. VII m = gm. Plasma Cholesterol Syn./Day
Subject of London & Rittenberg	? Chol.-Rich	12	3750	175	6.56	.546
No. 1	Chol.-Free	15.0	2990	218	6.5	.43
	Chol.-Rich	14.4	2990	261	(7.8-1.3)	.45
No. 2	Chol.-Free	11.6	2330	175	4.1	.35
	Chol.-Rich	12.3	2330	273	(6.4-2.3)	.33
No. 3	Chol.-Free	18.0	2891	150	4.3	.24
	Chol.-Rich	17.3	2891	193	(5.6-1.3)	.25
No. 4	Chol.-Free	13.7	3180	110	3.5	.26

molecule and is related to the rate at which serum cholesterol molecules are synthesized. It is interesting to note the relatively unchanged t ½ and $\bar{T}$* in both cholesterol-free and cholesterol-rich groups (Table 1).

A compilation of the data on all subjects and comparison with the data of London and Rittenberg indicate that the absence of cholesterol or the presence of 2.5 to 3.0 gm. per day in the diet results in no significant change in the t ½ or $\bar{T}$ of plasma cholesterol.

The estimated quantities of newly synthesized cholesterol appearing in the plasma each day are also reasonably comparable to the quantity reported by London and Tittenberg (Table 2). Again, the essentially complete lack of an effect of dietary cholesterol on estimated daily plasma synthesis is striking.

Conclusion

The above studies and our earlier studies indicate an essential absence of a "feedback" mechanism in man for compensation for dietary cholesterol. These studies suggest a continuous unaltered rate of delivery of endogenous cholesterol to the plasma regardless of diet. They further suggest that absorbed dietary cholesterol is added to endogenous serum cholesterol, resulting in a net higher serum cholesterol concentration. There still remains another important, incompletely studied facet of cholesterol metabolism; this concerns the ability of man to alter his rate of conversion of cholesterol to bile acids and later fecal excretion of both bile acids and cholesterol to compensate for variable quantities of dietary cholesterol. Studies of this nature have been reported in dogs and six laboratories are actively studying this mechanism in man. Our laboratory has also begun studies in this area which, in our opinion, represents the only possible remaining mechanism of significance which man may have to compensate for absorbed dietary cholesterol.

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*$\bar{T}$ = turnover rate.

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The Patient's Duty — and the Doctor's

First, our duties to and about the Doctor; to call him in time, to trust him, to obey him, to be grateful to, and to pay him with our money and our hearts and our good word, if we have all these; if we have not the first, with twice as much of the others. Second, the Doctor's duties to us. He should be able and willing to cure us. That is what he is there for. He should be sincere, attentive, and tender to us, keeping his time and our secrets. We must tell him all we know about our ailments and their causes, and he must tell us all that is good for us to know, and no more.

— John Brown (1810-1882)

Primary Hyperparathyroidism

IT IS PARTICULARLY appropriate to review facets of calcium and parathyroid metabolism at a celebration honoring Dr. Gerald T. Evans because of his longstanding interest in mineral metabolism.

Hyperparathyroidism masquerades as many different diseases and can produce acute and sometimes rapidly fatal illness. The diagnosis depends entirely on precise clinical chemical data, but the recognition of the possibility of hyperparathyroidism depends on certain clues derived from clinical examination. There have been several articles in the recent literature describing the findings and course of hypercalcemic crisis due to hyperparathyroidism.[1-9] Experience with two patients with hypercalcemic crisis, another patient with pancreatitis, and a fourth with skeletal and renal symptoms will be presented because of certain instructive features.

Materials and Methods

Routine laboratory procedures were carried out. Alkaline phosphatase determinations were made using the King-Armstrong method.[10] Serum and urine calcium and magnesium determinations were made using the Zeiss flame photometer with a double monochromator,[11] and calcium determinations were also made using the EDTA calcein method.[12] The mean of serum calcium values in normals by the flame spectrophotometer is 10.2 ± .22 mg. per cent, and by the EDTA calcein method 9.66 ± .41 mg. per cent. The mean value of serum magnesium in normals is 1.77 ± .12 mEq./L. Phosphorus was determined by the Fiske and Subbarow method,[13] and creatinine and blood urea nitrogen values were determined using a Technicon auto-analyzer. Urinary hydroxyproline was determined by the Prockop and Udenfriend method.[14]

Case 1

A 47-year-old white married woman was admitted to the hospital on June 10, 1963. She had been profoundly weak for ten days. Seven days before admission she had fallen in the bathroom and sustained a bruise above her right eye. She was nauseated and vomited frequently. Her bowels had not moved for the preceding five days, but they had moved three times the day before admission. Twelve hours before admission she had cramps as well as constant pains in the calf muscles of both legs. In spite of vomiting she was able to drink water and carbonated beverages; so her urine output had not decreased. She had not felt well for months but had been able to take care of household duties. She was so lethargic that it was difficult to get details of history, and her mental status rapidly deteriorated.

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Causing Hypercalcemic Crisis and Acute Pancreatitis

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Examination

On examination her temperature was 37° C., her pulse rate 70, her blood pressure 140/90, and her weight 49.2 kg. She was very lethargic and so weak she could not stand without help. Her tongue and lips were dry and her skin turgor was poor. The optic discs were normal, the retinal arteries were of normal caliber, and there were no retinal hemorrhages. A small right periorbital hematoma was noted. The tympanic membranes of both ears were normal, and the nostrils were patent and free of exudate. The gag reflex was present. The lymph nodes were not enlarged. The neck was supple. The lungs were resonant throughout and breath sounds were normal. The heart tones were normal, and the rhythm was regular. Masses interpreted as feces were palpated in both right and left lower abdominal quadrants. The spleen and liver were not palpated. Pelvic examination revealed normal external and internal genitalia. Touch and superficial pain senses were intact. Biceps, triceps, quadriceps, and Achilles reflexes were symmetrical and brisk. Quadriceps and iliopsoas muscle weakness was marked.

Laboratory Findings

The hemoglobin was 14.8 and 15.0 grams per cent; the leukocyte count ranged from 21,400 to 24,800/cu.

TABLE 1
Blood Chemistry Values

Date	BUN mg/ 100 ml	Carbon Dioxide mM/L	Sodium mEq/L	Potassium mEq/L	Chloride mEq/L	Calcium Zeiss mg/100 ml	Calcium EDTA mg/100 ml	Phosphorus mg/ 100 ml	Alkaline Phosphatase King-Armstrong	Magnesium mEq/L
6/10/63										
1 p.m.	46	35	139	2.5	94					
6/11/63										
8 a.m.				2.6	106				10.5	2.15
6/12/63										
8 a.m.	40	30	143	3.4	105		24.0	3.3	9.8	
2 p.m.						27.0	27.0			
3 p.m.						28.4				2.8
4 p.m.						27.2				2.6
7 p.m.	Parathyroidectomy					25.6				2.6
6/13/63										
1 a.m.						22.0				1.5
7 a.m.	67			7.0		20.8				1.6
2 p.m.				7.5		21.2				

mm. with 92 per cent neutrophils, 4 per cent lymphocytes and 4 per cent monocytes. The blood glucose was 108 mg. per cent. Urinary excretion of hydroxyproline was measured on a specimen of urine collected for three hours immediately before surgery. The output was 33.3 mg. for three hours. If this value is extrapolated to a whole day, the excretion would have been 268 mg/24 hours. Cerebrospinal fluid protein was 61 mg. per cent. Serial laboratory data are recorded in Table 1 and electrocardiograms in Figure 1.

Progress

Her physical and mental status deteriorated rapidly. The weakness and other symptoms were ascribed to dehydration and hypokalemia. Although transient improvement lasting for about twelve hours resulted from hydration and potassium administration, on the day after admission she became more ill, was more lethargic and became confused and disoriented. During the period of fifty hours before operation, she received a total of 10.5 liters of fluid with 710 mEq. of sodium chloride, 300 mEq. of potassium chloride and 48 mEq. of magnesium sulfate. Her blood pressure fell to 90/70. She developed various cardiac arrhythmias: atrial flutter, premature contractions and nodal rhythm. On June 12 her serum calcium was found to be 24 mg. per cent, rising later that day to a high of 28.4 mg. per cent. A diagnosis of hypercalcemic crisis due, most likely, to hyperparathyroidism was made.

Treatment

She was treated with calcium-disodium edatate, hydrocortisone, and metaraminol for a three-hour period and then an exploration of the neck was carried out. A 9.7 gram parathyroid adenoma was removed from the region of lower pole of the left lobe of the thyroid. She did not regain consciousness after the operation; but she lived for about 20 hours. It became increasingly difficult to maintain her blood pressure. Her urine output rapidly decreased and total output was only 96 ml. after the operation. Because of a rapidly rising potassium and failure of the serum calcium to fall, peritoneal dialysis was instituted at 2:00 p.m. on June 13. However, her condition became progressively worse, her blood pressure could not be maintained with vasopressor agents and she died at 4:10 p.m.

Autopsy Findings

An autopsy was performed. The main features of this examination were: atelectasis of lungs with pulmonary edema, nephrocalcinosis, acute and chronic pyelonephritis and acute cystitis, metastatic myocardial calcification, eosinophil hyperplasia of pituitary, satellitosis,* chromatolysis, and myelin sheath degeneration of the brain.

Case 2

A sixty-four-year-old white married woman was admitted for the first time on April 28, 1964, for evaluation of chronic constipation, weakness and lethargy, heart trouble, persistent nausea and vomiting of two weeks' duration, and "nervousness." She gave a history of Bright's disease at age twenty-four, and she had had kidney difficulties since that time. She had been treated elsewhere during the preceding year for chronic cystitis. Her blood urea nitrogen was known to have been elevated for a minimum of one year before referral. There was no history of renal lithiasis or hematuria. She had complained of pain in the pelvis. A diagnosis of myocardial infarction had been made six to seven years earlier. She had been hospitalized elsewhere ten days

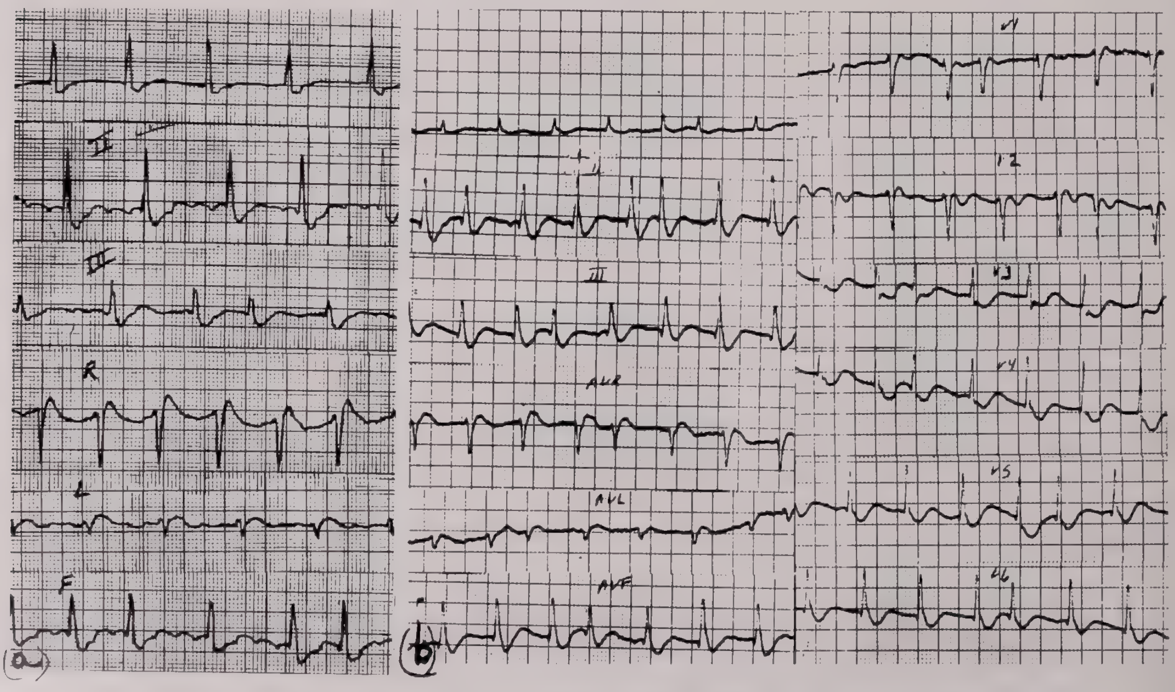

Fig. 1 — (a) Tracing taken 6/11/63 showing atrial flutter. (b) Tracing taken 6/12/63 showing nodal rhythm and bizarre ST intervals and T waves with short QT intervals.

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*See Test Your Word Score Page 779.

before referral and treated with diuretics because of peripheral edema, ascites, and paroxysmal nocturnal dyspnea with resultant loss of seventeen pounds of weight. Because of "anemia" she received a transfusion of two units of whole blood during that hospitalization. Medications at the time of admission included pentaerythritol tetranitrate, nitroglycerin, chlorothiazide, digitoxin (0.2 mg. daily), pentobarbital sodium, carbromal, and trimethobenzamide. Her family said that she had always been a demanding, complaining woman, and they suggested that she might have had hallucinations in the recent past. She had had a cholecystectomy at age 49.

Examination

Physical examination revealed a blood pressure of 128/80, a pulse rate of 80 per minute, respirations of 22 per minute and weight 44.6 kg. She was alert and oriented. There was bilateral corneal "band" keratopathy.* A diffuse non-nodular anterior neck mass rose on swallowing and extended substernally. The heart was enlarged to the left. The cervical veins were flat and the lungs were clear. The bowel sounds were active and there was minimal abdominal distention. There was marked generalized muscular weakness and mild dehydration.

Laboratory Findings

The urinalysis showed 1+ proteinuria and hyposthenuria with specific gravities of 1.004 to 1.010. The hemoglobin was 13.2 gm.%, hematocrit 41%. The leukocyte count was 12,600 with 86 per cent neutrophils, 13 per cent lymphocytes, 1 per cent monocytes. The sedimentation velocity was 24 mm./hour (Westergren). The VDRL was nonreactive and the BUN 63 mg. per cent with a creatinine of 3.2 mg. per cent. Serum bilirubin and bromsulfalein tests were normal. An arterial pH was 7.41 with pCO_2 of 37.5 mm. Hg. Urinary calcium excretion on the day before surgery was 148 mg./24 hours. Urinary excretion of hydroxyproline was 125 mg./24 hours. The results of serial tests are recorded in Table 2. A skeletal survey revealed a characteristic granular appearance in the skull and absent lamina dura. The pineal gland was calcified and showed no displacement. There was generalized demineralization with coarse bony texture and extensive periarticular calcification of the wrists, shoulders, hips and knees. The meniscus in the knees and the veins of the lateral aspect of the right lower leg were calcified. The Fallopian tubes appeared to be calcified. There was characteristic subperiosteal bone absorption of the proximal phalanx of the left index and middle finger. An electrocardiogram showed a markedly prolonged PR interval, intraventricular conduction defect and nonspecific T wave changes. The atrial rate was variable (Figure 2). An I^{131} uptake was 8 per cent at 24 hours. A thyroid scan, while technically imperfect due to the low uptake, indicated diffuse uptake over the left side of the gland but definitely less uptake on the right. A diagnosis of primary hyperparathyroidism was made.

Treatment

She was treated with intravenous fluids, potassium and sodium salts (primarily as the phosphate and lactate respectively). Digitalis was discontinued. Because she was well oriented and was improving with replacement therapy, her surgery was delayed until the third hospital day when her serum electrolytes were more nearly normal. At surgery a 6 cm. by 3 cm., 25 gram adenoma was removed from the right thyroid region. Microscopic section showed parathyroid adenoma of chief cell type. Her serum cal-

TABLE 2
Blood Chemistry Values

Date	BUN mg/ 100 ml	Carbon Dioxide mM/L	Sodium mEq/L	Potassium mEq/L	Chloride mEq/L	Calcium Zeiss mg/100 ml	Calcium EDTA mg/100 ml	Phosphorus mg/ 100 ml	Alkaline Phosphatase	Magnesium mEq/L
4/28/64	63	22	120	1.9	73		15.0	4.9	22	1.05
4/29/64	64		121	2.0	76		15.0	6.6		
4/30/64	95	29	126	3.4	82	16.4		6.4		2.0*
5/1/64	78	24	133	3.2	92	18.2	15.3		23.2	1.85
		Parathyroidectomy								
5/2/64	84	24	135	3.1	90	17.6	13.8			1.45*
5/3/64	88	29	137	3.9	93	15.8	12.2			1.1 *
5/4/64	80	31	140	3.9	87	15.3				2.05*
5/5/64		34	125	3.3	86	13.7	11.9			1.65*
5/6/64	58	29	127	3.2	81	13.2	10.8			1.55*
5/7/64	46					13.6	11.6			
5/8/64	37					12.6	10.7			
5/13/64	32					10.0				2.1
5/29/64	40						8.1	5.3		
6/9/64							6.9	5.5	11.9	
7/21/64							10.3			

*Mg SO_4 was given intramuscularly.

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*See Test Your Word Score Page 779.

cium remained elevated for eleven days postoperatively. Eighteen days postoperatively her serum calcium fell to 8.3 mg. per cent and she developed mild paresthesias. On the twentieth postoperative day her serum calcium was 7.1 mg. per cent, phosphorus 6.0 mg. per cent, and she was given small doses of Calciferol with subsequent maintenance of her serum calcium in the 8 to 9 mg. per cent range.

Progress

Her BUN progressively fell to 32 mg. per cent by the tenth postoperative day. Repeat electrocardiograms revealed gradual diminution of the PR interval. Because of cardiomegaly and a past history of congestive heart failure, she was again given digitoxin. Desiccated thyroid was started. Aside from one period of hallucinations and paranoia shortly after surgery, her postoperative course was uncomplicated.

Outpatient follow-up visits have shown the need of diuretics to control fluid retention. Calciferol has been stopped and her serum calcium remains in normal range. Mild constipation is now easily controlled with occasional cathartics.

Case 3

A twenty-five-year-old white married woman was admitted July 8, 1963, to the hospital for evaluation of hypercalcemia and a history of recurrent pancreatitis. She was working regularly as a nurse until the time of her admission. She had enjoyed good health all her life until age twenty-one when she developed preeclampsia in the seventh month of her first pregnancy, terminating with a still birth one month later. She was again well, but in the following two years she developed pneumonia which was successfully treated with chloramphenicol. Subsequently, she had a bout of acute pancreatitis. An upper gastrointestinal study and a cholecystogram following the acute illness were normal. A second pregnancy was terminated by Cesarean section near term because of abruptio placenta. A viable infant was delivered. He had no convulsions during infancy. Ten months before her admission she had a second bout of acute pancreatitis. Following this, she returned to her usual state of health. At the time of her admission she had no specific complaints but was admitted because an elevated serum calcium was found in an effort to explain her episodes of pancreatitis. On specific questioning she admitted having decreased energy for the preceding two to three years and polydipsia and polyuria for as long as two years. Frequent dull occipital headaches had been present for the preceding two months. She denied visual disturbances. She had never had renal or urinary tract symptoms. There had been no nausea, vomiting, diarrhea, or constipation. Her two male siblings and her parents were in good health.

Examination

On physical examination she was a healthy appearing young woman, 170.5 centimeters tall and weighing 64.4 kilograms. The vital signs and the physical examination were entirely normal. No neck masses were palpated.

Laboratory Findings

A urinalysis showed a specific gravity of 1.015 and a faint trace of albumin; red blood cells were present, and there were fairly numerous granular casts. The hemoglobin was 13.6 gm. per cent with a 41 per cent hematocrit. There were 5,500 leukocytes with 54 per cent neutrophils, 42 per cent lymphocytes, 1 per cent eosinophils and 3 per cent basophils. Wintrobe sedimentation rate was 6 mm. in one hour. Blood urea nitrogen was 18.5 mg. per cent. Multiple serum calcium determinations ranged between 14.2 mg. per cent and 16.0 mg. per cent, and phosphorus from 1.6 to 2.5 mg. per cent. The total serum protein was 7.6 gm. per cent with 4.5 gm. per cent albumin, and 3.1 gm. per cent globulin. Alkaline phosphatase was 12.3 King Armstrong units. Sodium, potassium, chloride and CO_2 determinations were all normal. Plasma magnesium ranged between 1.55 and

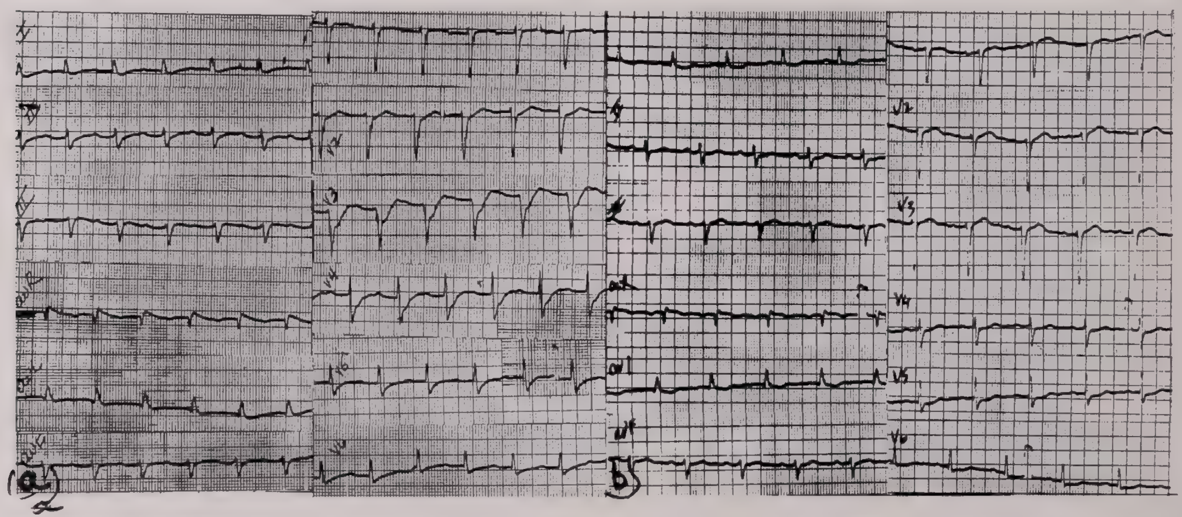

Fig. 2 — (a) Tracing taken 4/30/64 showing prolonged PR interval and bizarre ST segments. (b) Tracing taken on 5/11/64. PR now normal and T and ST changes have disappeared.

2.0 mEq/L. Urinary calcium excretion ranged from 594 to 712 mg./day on three consecutive days. Additional laboratory data are recorded in Table 3. Radiographic examination of the chest was normal and an esophagogram showed no displacement of the esophagus. Films of the hands were normal. An electrocardiogram was normal. The phosphorus excretion pattern was not altered by calcium infusion, (positive Goldsmith test).[15] A diagnosis of primary hyperparathyroidism was made and confirmed at surgery.

Treatment and Progress

A 1.2 x 1.2 cm. adenoma was excised from the left side of the neck, adjacent to the inferior pole of the left lobe of the thyroid gland. Histologic sections showed it to be a chief cell adenoma. Her postoperative course was smooth. The serum calcium reached normal levels on the third postoperative day. There was no hypocalcemia following surgery. She has returned to work, and serum calcium levels six and twelve months after surgery have been normal. She delivered a normal child after an essentially uneventful pregnancy just thirteen months after surgery. She is now in her fourteenth postoperative month and continues to be in good health.

Case 4

A 62-year-old white married woman was referred to this hospital on February 3, 1964, with a diagnosis of probable hyperparathyroidism. On admission she complained of pain in her bones and nervousness.

Because of pain in her back and extremities a diagnosis of rheumatoid arthritis had been made in 1951. She had episodes of acute renal colic without recovery of stones in 1954 and again in 1955. In 1958 she began having recurrent urinary tract infections. During this period she passed multiple urinary calculi and one year before admission a ureteral stone was removed surgically. About that time an intravenous urogram had failed to visualize the kidneys. In the last six months she had had increasing pain in her back and extremities, but there was no associated joint swelling. She had been treated for episodic diarrhea and on admission she was being treated for glaucoma. She had a right salpingo-oophorectomy at age 28 and cholecystectomy at age 38. There was no history of peptic ulcer, pancreatitis, or polydipsia. She had muscle weakness and intermittent headaches on the right side.

Because of persistent bone pain and the history of recurrent urinary tract disease, her physician measured her serum calcium and found it to be elevated.

Examination

On admission she was alert, ambulatory, and oriented. Her blood pressure was 126/88 and her pulse was regular, varying between 70 and 88 per minute. She weighed 58.8 kg. Examination of the eyes showed normal pupils and fundi, but cupping of the temporal margin of the optic disc was noted bilaterally. Keratopathy or cataracts were not detected. She was edentulous. The thyroid gland was normal except for a single nodule in the left lobe. There was dorsal kyphoscoliosis, the chest was clear to auscultation and percussion, and there was tenderness to palpation over the left anterior thorax. Examination of the heart was normal except for a Grade I systolic murmur at the apex. There were well healed abdominal surgical scars. Pelvic examination was normal. The extremities were normal without any evidence of joint deformities.

Laboratory Findings

Laboratory studies included a hemoglobin of 11.0 gm. per cent, an erythrocyte count of 4.5 million, an hematocrit of 34.5 per cent, and a leucocyte count of 8,800/cu. mm. with 59 per cent neutrophils, 37 per cent lymphocytes, 4 per cent monocytes. The Wintrobe sedimentation rate was 20 mm. in one hour. The specific gravity of urine was 1.008, the pH 7.0; there were 2-3 WBCs per high power field and 1-2 casts/low power field. There was no proteinuria or glyco-

TABLE 3

	Blood Chemistry Values					Urine Chemistry Values				
Date	BUN mg/100 ml	Calcium Zeiss mg/100 ml	Calcium EDTA mg/100 ml	Phosphorus mg/100 ml	Magnesium mEq/L	Calcium mg/d	Magnesium mEq/d	Phosphorus mg/d	Phosphorus Clearance ml/min	Creatinine Clearance L/d
6/13/63		14.8	14.7	2.1	2.1					
6/27/63		16.0		1.6	1.8					
7/8/63	16		14.3	2.5	1.95	594	9.3	990	31	95
7/9/63						712	10.3	1023	36	80
7/10/63						690	16.9	976	41	
7/11/63		Parathyroidectomy								
7/12/63			10.7							
7/13/63		11.0		1.6	1.55					
7/14/63			10.6	3.2	2.0					
7/15/63	23	9.4	9.1	3.6	1.85	76				108
7/17/63	18	10.0				77			18	
12/31/63		10.8		3.8	1.9					
7/6/63		10.0								

suria. The BUN was 17 mg. per cent. The sodium, potassium, chloride, and carbon dioxide were normal. The serum creatinine was 1.1 mg. per cent and an alkaline phosphatase was 10.1 K.A. units. There were 6.9 gm. per cent total serum proteins with 3.7 gm. per cent albumin and 3.2 gm. per cent globulin. Serum calcium determinations ranged from 14.8 to 16.8 mg. per cent (Zeiss) and phosphorus from 1.7 to 1.88 mg. per cent. A calcium infusion did not change the phosphorus excretion (positive Goldsmith test).[15]

A radiographic survey of the skeleton showed extensive generalized demineralization compatible with hyperparathyroidism. An electrocardiogram was normal. A diagnosis of primary hyperparathyroidism was made and confirmed at the time of surgery.

Treatment and Progress

A 3.0 by 1.0 by 1.0 centimeter nodule weighing 3.0 gm. was removed from an area adjacent to the inferior pole of the left lobe of the thyroid. Histologically this was a parathyroid adenoma composed of an admixture of chief cells and clear cells.

Her surgery and postoperative course were uncomplicated except for a drop in hemoglobin to 8.4 gm. per cent by the eighth postoperative day. There was no excessive blood loss at surgery nor was any other source of bleeding found. By 23 days after surgery the hemoglobin had risen to 10.0 gm. per cent.

She was seen two months after surgery, at which time she was feeling well. She had had no symptoms suggestive of hypocalcemia. Subsequent to that time she has failed to return to clinic for further evaluation.

Discussion

Parathyroid hormone has multiple actions.[16] Some of the activity undoubtedly is the result of shifts in equilibrium reactions. Parathyroid hormone increases the absorption of calcium from the small intestine; for this action Vitamin D is also necessary. At the cellular level it: (1) inhibits oxidative phosphorylation of isolated liver mitrochondria, (2) increases the aerobic lactate production of bone slices in vitro, (3) increases the turnover of various organic phosphate esters and the phosphoproteins of the kidney, (4) increases the P^{32} and Ca^{45} transport in isolated loops of intestine, and (5) inhibits uptake of radioactive glycine C^{14} by bone grown in tissue culture. It increases citrate, phosphate, potassium and sodium excretion and decreases hydrogen ion excretion by the kidney. It increases renal tubular reabsorption of calcium; the paradoxical* increased excretion of calcium in hyperparathyroidism is the result of increase in total and ultrafilterable serum calcium. Therefore the increase in calcium of glomerular fluid results in a net increased excretion of calcium. During in-vitro incubation of bone preparations, the hormone causes disappearance of typical osteoblasts, the formation of multinuclear osteoclasts, the dissolution of bone matrix, and changes in epiphyseal cartilage and connective tissue pattern. Parathyroid hormone mobilizes calcium from bone. It has an effect on ground substance of bone and on the production of citric acid and lactic acid by bone cells.

TABLE 4

	Blood Chemistry Values						Urine Chemistry Values	
Date	BUN mg/ 100 ml	Creatinine mg/ 100 ml	Alkaline Phosphatase King-Armstrong	Calcium mg/ 100 ml Zeiss	Phosphorus mg/ 100 ml	Magnesium mEq/L	Urine Calcium mg/d	Phosphorus Clearance ml/min.
2/4/64	17		10.1	14.8	1.7		260	
2/6/64		1.0		16.4	1.94	2.2	288	
2/7/64		1.1		16.8		1.88		26
2/9/64		Parathyroidectomy		15.8	1.88	2.15		
2/13/64				13.6		1.85		
2/14/64				12.4		1.83		
2/15/64				10.5		1.95		
2/16/64				10.1		1.85		
2/18/64				10.1		1.75		
2/20/64				10.2		1.5		
2/21/64				8.9	3.8	1.6		
				9.9	2.8			

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*See Test Your Word Score Page 779.

Calcium Intoxication from Parathyroid Hormone

There have been at least 29 deaths due to acute calcium intoxication (1, 5, 9, present case). The course of illness has been characteristic, with fulminating progress beginning with profound muscular weakness and progressing to hypotension and death in the course of seven to fourteen days unless it is recognized and treated. Although a few instances have occurred in childhood and early adult life, the majority of instances have occurred after the age of 40. The most important symptoms are muscular weakness, nausea and vomiting, weight loss, lethargy, confusion and other evidence of delirium, abdominal pain, polyuria, polydipsia, constipation and coma. Bone pain and renal colic also occur frequently but are not constant or prominent symptoms in the majority. Obviously, any symptom which acts as a clue is worthy of note. The emphasis rests on muscular, gastrointestinal and mental symptoms in hypercalcemic crisis.

Patient 1 demonstrated most of the features of acute calcium intoxication. Her illness was recognized late in its course. Shock was irreversible in the postoperative period.

Patients 1 and 2 both had leukocytosis. In Patient 1 the very high leukocyte count resulted in a great deal of effort to find an infectious process. Leukocytosis of this degree has been reported.[3,7] This finding could lead to an erroneous diagnosis or at least to fruitless diagnostic efforts. The mildly elevated spinal fluid protein is indicative of central nervous system irritation and has been reported before.[1] Again this laboratory finding can be misleading in a patient with profound central nervous system symptoms suggesting an acute neurosurgical problem.

Palpable Mass

The finding of a neck mass has been reported in 42 per cent of cases.[1] In Patient 2 a mass interpreted as a goiter was palpated. She had symmetrical enlargement in the region of her thyroid gland. An I^{131} scintogram of her neck revealed the concentration of iodine predominantly on the left side. One possibility, therefore, was that the mass on the side opposite that concentrating I^{131} was actually a parathyroid adenoma. This proved to be true, but this possibility was only casually hinted at before identifying the adenoma. An I^{131} thyroid scintogram could prove to be useful in identifying adenomas in the thyroid gland, impinging on it or displacing it just as esophagograms and arteriograms have proved to be useful.

Electrocardiographic Findings

Electrocardiographic changes in Figures 1 and 2 are typical of those previously published.[4,5,17,18] The changes in electrocardiograms in Figure 2 are less severe than those in Figure 1. The changes disappear after calcium returns to normal. The tracings suggest hypokalemia because of the bizarre, sagging ST segments; but the QT interval in hypercalcemia is very short, and the PR interval is prolonged. Electrocardiographic changes in hyperparathyroidism were first suggested in 1932 by Ballin[19] and were more clearly defined in 1936 by Kellog and Kerr.[20] In 1956 Bradlow and Segel[4] published a definitive account of electrocardiographic changes. The most characteristic of these changes are prolonged PR interval, shortened QT interval, sagging of the ST takeoff and shortening and straightening of the ST interval so that QaT interval (Q to apex of T) is particularly short.[17] Patients 1 and 2 both exhibited rather striking changes. The arrhythmias which occurred in Patient 1 are potentially dangerous, and some patients with severe hypercalcemia undoubtedly die as a result of serious rhythm disturbances. Although electrocardiographic changes such as prolonged PR and shortened QT intervals are often described, relatively few reproductions of electrocardiograms have been published.[4,5,17,18] The changes are striking and worthy of reproducing, since some of them are difficult to describe. Figures 1 and 2 may serve as a clue for recognition of other cases of calcium intoxication. The similarity of findings and reversion toward normal as noted in Figure 2 are convincing evidence of the diagnostic value of these changes. Patients 3 and 4 had normal electrocardiograms.

Electrolyte Disturbances

Potassium disturbances have been noted recently. Three of four patients reported by Lemann and Donatelli[1] had hypokalemia. Both Patients 1 and 2 had hypokalemia. Patient 2 had been treated with chlorothiazide, but Patient 1 had received no medications. Potassium wastage by the kidney could be due entirely to renal damage by hypercalcemia as suggested by studies on Vitamin D intoxication.[21] Poor food intake certainly contributed to a net loss. Parathyroid hormone increases potassium excretion by the kidney, so this action undoubtedly could contribute to potassium depletion.[16]

Magnesium depletion has been documented in patients with hyperparathyroidism by demonstration of a significantly positive magnesium balance after parathyroidectomy[22] and by recognition of magnesopenia following parathyroidectomy with attendant nervous and mental symptoms.[23,24] The delirium following parathyroidectomy recently reported[25] was not due to hypocalcemia, but could have been due to magnesium depletion. Delirium following parathyroidectomy is fairly common and magnesium depletion is an important cause. A balance study of Patient 2 revealed a distinctly positive magnesium balance during the first twelve postoperative days. She developed mild delirium with paranoid ideas on the fourth postoperative day. Her serum magnesium dropped to a low of 1.15 mEq./L. on the second day, after which time she received small doses of magnesium on days 3, 4, 5, 6, 8, and 9. A positive balance of 35.8 mEq. or 0.9 mEq./Kg. magnesium occurred in 12 days.

Differential Diagnosis

The differential diagnosis of hypercalcemia includes sarcoidosis; vitamin D intoxication; lymphoma; Hodgkin's disease; multiple myeloma; metastatic cancer to bone; carcinoma of lung, kidney, ovary, or pancreas without skeletal metastasis; and skeletal immobilization following fracture of large bones, especially in Paget's disease and in adolescents. In instances of hypercalcemia without serious systemic symptoms it is worthwhile to administer cortisone (or related steroid) for a week and follow the serum calcium level. In most patients with hypercalcemia due to causes other than hyperparathyroidism, cortisone will lower calcium to or toward normal. Occasionally patients with hyperparathyroidism also respond to cortisone with lowering of calcium to normal.[26,27] Hypercalcemic crisis is so serious that delay for observation of cortisone effect is not warranted. Emergency surgery is indicated, unless it already has been clearly established that the hypercalcemia is due to another cause.

Medical Management

The administration of calcium disodium edatate or citrate has theoretical value. Both were used in the first patient. Calcium disodium edatate has been found to be nephrotoxic. Neither citrate nor calcium disodium edatate had any appreciable effect. Albright, Bauer, Chaflin and Cockrill[28] showed that a high phosphate and low calcium intake lowered serum calcium in hyperparathyroidism. However, such a program should not be used as a long-term treatment because it could enhance metastatic calcification. A low calcium (100 mg/d) and high phosphate diet was used by Bradlow and Segel[4] for ten days, with lowering of calcium and BUN and remarkable improvement in one patient. Dent[26] has used 10 to 15 grams of sodium phosphate orally daily with distinct lowering of calcium levels. A total of 230 mEq. of potassium phosphate was administered in two days to Patient 2 preoperatively. During the operation and postoperatively, sodium lactate was infused because of the demonstration that lactate enhances excretion of divalent cations.[29] Sodium sulfate has been recommended because sulfate ion enhances divalent cation excretion.[30]

Sequellae

Pancreatitis is an important associated illness and one which should suggest hyperparathyroidism, particularly in patients who have no apparent illness such as cholelithiasis or alcoholism. Up to 1962 Mixter, Keynes, and Cope[31] were able to collect 62 cases of hyperparathyroidism and pancreatitis. Pancreatitis may complicate acute parathyroid crisis.[1,7] Ten of 380 patients at the Mayo clinic had pancreatitis.[32] The occurrence of two bouts of pancreatitis in Patient 3 was the clue which led to the diagnosis of hyperparathyroidism. In acute pancreatitis the serum calcium may fall to low levels and tetany occur. During an episode of acute pancreatitis, therefore, a normal or even low serum calcium does not exclude hyperparathyroidism. It is important to determine the serum calcium in a symptom-free interval in order to avoid values lowered transiently by the acute pancreatitis. The symptoms of pancreatitis have been corrected for more than a year in Patient 3. Amelioration of symptoms of pancreatitis after correction of hyperparathyroidism can be anticipated.[31] Pancreatitis has occurred in several patients with familial hyperparathyroidism.[33]

Neonatal hypocalcemia with infant convulsions has been reported occasionally in children born of mothers with hyperparathyroidism,[34] but this was not a problem in the child of Patient 3. Although it cannot be stated categorically that the fetal death and premature separation of the placenta in the three years before operation in Patient 3 were due to hyperparathyroidism, the successful and uneventful pregnancy since parathyroidectomy strongly suggests this relationship. Reports of pregnancies complicated by hyperparathyroidism indicate that fetal death and the other complications may occur with greater frequency than expected.[34] Parathyroid hormone has an effect on ground substance and could cause increased ease of placental separation. An interesting case has recently been reported by Preston and Adicoff[35] of avulsion of the patellar and triceps brachialis tendons in a patient with hyperparathyroidism. This can also be ascribed to the effect of parathyroid hormone on ground substance and connective tissue in general.[36] The greatly increased hydroxyproline excretion in hyperparathyroidism has been confirmed in two of our patients. Many factors influence hydroxyproline excretion. Excretion is increased by growth hormone, parathyroid hormone, and during periods of rapid growth during puberty.[9,37,38,39] Calcium infusion in patients with hyperparathyroidism[39] and in a patient with hypoparathyroidism[37] produced no fall in hydroxyproline excretion. However, calcium infusion in normal persons produces a fall in hydroxyproline excretion.[37] Contrary to the report of Klein, Albertson, and Curtiss,[7] Patient 1 had a normal level of alkaline phosphatase but, nevertheless, had a very high excretion of hydroxyproline. The second patient did have a modest increase of alkaline phosphatase and also an elevated hydroxyproline excretion.

In the Mayo Clinic experience, Keating reports that 64 per cent of their 380 patients had presenting symptoms indicative of renal calcinosis, and that another 12 per cent had associated symptoms referrable to urinary calcinosis. The history of renal stones and renal infections as well as bone pain in Patient 4, therefore, is the usual or expected one. Keating points out that hypercalcemia may be trivial in some instances. Fifty-two patients proven to have hyperparathyroidism at operation had one or more calcium values within the normal range preoperatively. The serum phosphorus was less reliable than the calcium. Goldsmith[15] has reviewed experience with a calcium infusion test which he devised. Infusion of 180 mg. of calcium interrupts the normally occurring rise in phosphate excretion during the morning hours, but not in hyperparathyroidism. He reports twenty patients with a positive test, all of whom proved to have hyperparathyroidism, although some had normal serum calcium and phosphorus values. As hypercalcemia was marked in all our patients, phosphorus clearance tests were not really necessary. The Goldsmith test was positive in the two patients so tested.

Multiple endocrine adenomas of the pituitary, the parathyroid, and the pancreatic islet cells occur in the same patient and may occur in families.[32,33] Hyperparathyroidism may occur with the Zollinger Ellison syndrome.[32] One should be alert to the possibility of the development of an adenoma of one or the other of the three glands in a patient who is being treated or has been treated for an adenoma of one of these glands.[40]

Summary

During a one-year period the diagnosis of hyperparathyroidism was confirmed in four patients.

One patient died of hypercalcemia crisis. She had a fulminant course of illness. Another patient had similar symptoms but was less severely ill and recovered following parathyroidectomy. Both patients had nausea and vomiting, mental symptoms, constipation, profound weakness, hypokalemia, azotemia, leukocytosis, and characteristic electrocardiographic changes. The first patient developed delirium and finally became comatose. Suggestions are made for the management of crises.

The third patient had several attacks of acute pancreatitis and had had serious complications of pregnancy on two occasions (fetal death once and abruptio placentae once). She also had pronounced weakness, thirst, and polyuria. A fourth patient had a more characteristic course with recurrent renal colic and bone pain. She also was very weak.

A drop in serum magnesium levels after surgery occurred in three patients and one had a low level initially. Postoperatively a magnesium balance was measured in this patient and was positive.

Addendum

Since submission of the manuscript, a paper entitled "Inorganic Phosphate Treatment of Hypercalcemia of Diverse Etiologies" (NEW ENGLAND JOURNAL MEDICINE 274:1, 1966 by R. S. Goldsmith and S. H. Ingbar) defines a practical and effective procedure for treating hypercalcemic crisis.

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13-39 May be secured from the author or the reprints.

MILK DRINKER'S SYNDROME (Burnett's Syndrome)

During excessive milk alkali therapy for peptic ulcer, hypercalcemia, alkalosis and transient renal insufficiency with azotemia may develop to cause this syndrome. The excessive use of milk, cream and calcium carbonate may in some individuals cause symptoms of headaches, nausea, vomiting, anorexia, dizziness, irritability, mental confusion, depression, ataxia, stupor and toxic psychosis in progressive order. Serum phosphorus and alkaline phosphatase levels are normal and absence of skeletal demineralization aids in differentiating this from primary hyperparathyroidism.

Durham, Robert H. — Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

When one gets older his clothes run to more latitude than to longitude.
— Herbert Prochnow

Structure and Function of the Lung

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PULMONARY EMPHYSEMA is characterized by destruction of the normal architecture of the lung. Alveolar septa are lost, and the normal air spaces are replaced by larger air-containing structures of variable size. Attention has focused on the normal architecture of the lung and its relation to function. Structure and function are of necessity closely related, and one cannot be understood without knowledge of the other.

The size of the terminal air spaces is of particular importance in the functioning of the lung. D'Arcy Thompson[1] in his excellent discussion of the relationship between structure and physical forces has emphasized the importance of magnitude. Taking L as the linear dimension of any object, and assuming that the size of the object varies but not the form, then the surface area will be proportional to the square of L, and the volume will vary with the cube of L. Thus each time L is doubled, there occurs a fourfold increase in area but an eightfold increase in volume. As a result, and because weight is a function of volume, large solid objects have a small surface area relative to their mass, and small objects a relatively large surface area. The force of gravity and the strength of structure and materials limit the size of large animals and plants. Surface tension becomes an important force in the functioning of small organisms. The power of surface forces can be observed on any pleasant summer day by examining the behavior of insects on the surface of a quiet pond.

The Surface Area of the Lung

The Diffusing Capacity

The function of the lung is to supply oxygen and to remove carbon dioxide from the blood. If the human lung were a simple sac the surface area would be small and the diffusing capacity extremely low. The diffusing capacity is usually measured by determining the uptake of carbon monoxide by the lung and is expressed as the volume of a gas which is transferred in a given period of time from alveolar air to capillary blood divided by the gradient of gas tension between the alveolar air and the blood.[2] The diffusing capacity is dependent on the surface area of the lung as well as on the thickness of the membrane separating the alveolar air and capillaries. If the diffusing capacity for oxygen is abnormally low, the hemoglobin of the pulmonary arterial blood will not be saturated with oxygen during its passage through the pulmonary capillaries.

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The Surface Area

The human lung is, of course, not a simple sac but is divided into small air spaces (alveoli) by innumerable septa, which greatly increase the surface area available for diffusion of gases. They are richly supplied with capillaries to permit this exchange of gas. Recent studies by Weibel[3] have shown the surface area of the adult human lung to measure approximately 75 square meters. The average diameter of the alveoli is 275 micra. If the lungs are destroyed by disease or if the septa are lost as in pulmonary emphysema the diffusing capacity of the lung decreases.

The division of the lung into innumerable small spaces with the consequent high ratio of surface area to volume brings the forces of surface tension into play. Surface forces are present whenever an air fluid interface is created. Work is required to create this interface and work can be recovered if the surface shrinks and the surface area decreases. Thus, a surface possesses free energy or the power to do work. The energy involved is proportional to the magnitude of the surface area.

Much of the elastic behavior of the lung is a result of this surface energy. This can be demonstrated by filling the lung with water which eliminates the air fluid interface and alters the elastic behavior. Relatively normal elastic behavior can be demonstrated in the air-filled excised lung even though tissue elasticity has been destroyed by treatment with alkali and elastase.[4]

The magnitude of the surface forces will depend on the nature of the air fluid interface. The surface tension of pure water is 72 dynes per cm. but is lowered considerably if a protein or oily film is present on the surface of the fluid. A lipid film is present at the air fluid interface in the alveoli, and this modifies the surface forces and influences the elastic behavior of the lung.[5] The presence of this film lends stability to the air-filled spaces and prevents collapse of spaces during normal function of the lung.

There is another advantage in the presence of small air spaces in the lung. Movement of gases in the terminal air spaces is by diffusion. If the air spaces were large a significant gradient of gas tension would exist. The small size of the alveoli reduces this gradient to an insignificant amount.

The Structure of the Alveolar Wall

The function of the alveoli is to permit ready exchange of oxygen and carbon dioxide between alveolar air and blood. To accomplish this the alveoli must be well ventilated with air, and the walls of the alveoli abundantly perfused with blood. Anatomic studies of the lung demonstrate numerous capillaries in the walls of the alveoli so that the walls appear to consist of a sheet of blood.

Separating the capillaries from the alveolar air is the alveolocapillary membrane. Electron microscopy has elucidated the nature of this structure.[6] The wall consists of the capillary endothelium with its basement membrane, the intermembranous space containing collagen and elastin, and the alveolar lining cells with their basement membrane. The most important observation is the remarkable thinness of the whole structure (average 1.3 micra).[3] This permits the ready diffusion of oxygen between alveolar air and capillary blood and, together with the huge surface area of the interior of the lung, allows for the large diffusing capacity of the lung.

The Connective Tissue Fibers of the Lung

The lung is not simply a series of small bubbles but has a solid structure which is constantly subjected to forces as the lung expands and recoils. If the lung did not contain structures with elasticity and high tensile strength the form could not be preserved over the lifetime of the individual. The connective tissue fibers in the lung serve such a purpose. These fibers are composed of fibrous proteins, collagen and elastin and form a network about the air-containing structures. The collagen fibers have high tensile strength, short range elasticity and a high modulus of elasticity. The elastin fibers are of lower tensile strength and have long-range rubber-like elasticity. The fibers are arranged in a helical* pattern about the alveolar ducts. This springlike arrangement permits collagen as well as elastin to contribute to the elastic properties of the lung.

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*See Test Your Word Score Page 779.

The integrity of this network is essential to the normal structure and function of the lung but is often lost in the lungs of aged individuals. Increase in size of the air spaces, loss of septa and formation of abnormal air spaces result. The term emphysema is used to describe this process.

The Conducting of Airways of the Lung

The trachea and bronchi serve as passive conduits to permit movement of air to and from the lungs. The resistance to air flow is dependent on the size of these structures. The trachea is 2 cm. in diameter whereas the terminal bronchioles are 0.6 millimeters in diameter.

Resistance to Air Flow

Intuitively one would think that the resistance to air flow in the smallest bronchi would be very great. This is not true. The resistance to flow is dependent not only on the size of the airways but on the velocity of air flow. If the total cross-sectional area of all the terminal bronchioles is very large, as indeed it is,[3] then the velocity of air flow will be small. One can make an analogy to the capillary bed of the vascular system where the vessels are tiny, the flow is slow, and the resistance not great. The location of increased resistance in diseases associated with diffuse bronchial obstruction such as bronchitis and bronchial asthma is quite another matter. Small bronchi can be obstructed and offer great resistance to flow.

Bronchial Obstruction

When bronchial obstruction is present the expiratory phase of breathing is predominantly affected. Inspiration may be accomplished with little difficulty. The explanation for the predominant expiratory nature of the obstruction in bronchitis and asthma is found in the structure of the lung. The larger bronchi contain plates of cartilage but in spite of this can undergo partial collapse with external pressure. The smaller bronchi have no supporting cartilage. The intrapulmonary bronchi are surrounded by air spaces as shown in Figure 1. Attached to the bronchi are connective tissue fibers which are part of the fibrous network of the lung. These connective tissue fibers exert traction outward and tend to expand the bronchi. The force exerted by these fibers will be a function of the degree of inflation of the lung. The difference in pressure between the alveoli (P_1) and lumen of the bronchus (P_2) will distend the bronchus during inspiration when the intra-alveolar pressure is negative and will tend to collapse the bronchus during expiration when the intra-alveolar pressure is positive. If bronchial obstruction is present and if expiration is forced, a large gradient will exist between the alveoli and bronchus, and P_1 will greatly exceed P_2. If the force created by this pressure difference exceeds the outward force from the fibrous network of the lung the bronchus will collapse. It is more likely to collapse when the lung is partially deflated than when it is fully inflated, because the tension exerted on the bronchus by the connective tissue fibers increases with increased inflation of the lung. Thus, the structure of the lung explains the familiar expiratory wheezing and the phenomenon of air trapping associated with bronchial obstruction.

Conclusion

The normal function of the lung is to a large extent dependent not only upon the anatomic arrangement of the structures but also upon their magnitude. The magnitude of the alveolar spaces permits the exposure of

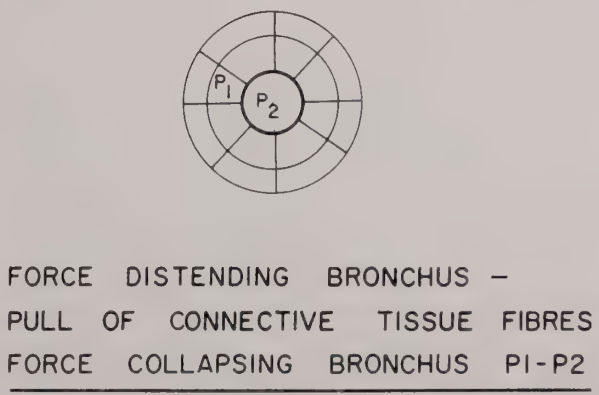
P1
P2
FORCE DISTENDING BRONCHUS –
PULL OF CONNECTIVE TISSUE FIBRES
FORCE COLLAPSING BRONCHUS P1-P2

Fig. 1 — Forces impinging on a bronchus. The center circle represents the bronchus. The radiating lines represent connective tissue fibers. The spaces about the bronchus such as that labelled P_1 represent alveoli.

an enormous surface for exchange of oxygen between air and blood. The size of these spaces and their great surface area make surface energy an important determinant of lung function. The relationship between the size of the bronchi and the flow through them determines the resistance to movement of air. The thinness of the alveolocapillary membrane together with the great surface area of the lung permits the exchange of large volumes of oxygen during exercise without the development of hypoxia.

Diseases which modify the magnitude of these structures will result in malfunction of the lungs. Pulmonary emphysema consists of a loss of the normal structure of the peripheral air spaces. As one would surmise from the relationship between structure and function the disease produces profound changes in the function of the lungs.

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IT'S THE LAW

Tests of Infants for Inborn Metabolic Errors Causing Mental Retardation

It is the duty of (1) the administrative officer or other person in charge of each institution caring for infants 28 days or less of age and (2) the person required in pursuance of the provisions of Minnesota Statutes, Section 144.159, to register the birth of a child, to cause to have administered to every such infant or child in its or his care *tests for phenylketonuria and other inborn errors of metabolism causing mental retardation* in accordance with rules or regulations prescribed by the state board of health. The provisions of this section shall not apply to any infant whose parents object thereto on the grounds that such tests and treatment conflict with their religious tenets and practice.

Effective Date. This act is effective on July 1, 1965.

The Physician's Rewards

By his training, by the human, moral and priestlike nature of his function, by the confidence he inspires and the gratitude he often deserves, the physician is one of the chiefs among the people. That is the way it has been and I do not see that it will ever be any different, no matter what changes are made in the political and social structures of our societies.

— Georges Duhamel (1844-)

Bad men live that they may eat and drink, whereas good men eat and drink that they may live. — Socrates

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The people who get on in this world are the people who get up and look for the circumstances they want, and, if they can't find them, make them.

— George Bernard Shaw

Quantitative Urine Culture with Calibrated Bacteriologic Loop

Office Laboratory Technique

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QUANTITATIVE URINE cultures provide clinicians with a means for specific, accurate diagnosis of urinary tract infections. Because of the insidious, occult, and persistent aspects of some urinary tract infections, generous use of this method is indicated and calls for techniques which are simple, inexpensive, and potentially available to any laboratory including that of the doctor's office.

Routine use of quantitative urine cultures seems particularly applicable to a "high-risk population," notably diabetic, hypertensive, and gravid patients; or to a "suspect population," such as infants and children with fevers of unknown origin or failure to thrive; or, indeed, to apparently normal children and adults as part of routine medical evaluation.

It is the purpose of this paper to present a simple method for quantitating urine cultures, first described by Hoeprich[1] for use in hospital laboratories, utilizing a standard, calibrated bacteriological loop.

Methods

One hundred thirty-five urine specimens submitted for routine culture to our hospital diagnostic bacteriology laboratory were selected for parallel quantitative culture by the tube dilution and the calibrated loop method. Eosin-methylene blue and sheep blood agar petri plates comprised the diagnostic media used in each instance. Gram-stained smears were also obtained on 95 specimens cultured by the tube dilution and loop methods.

The tube dilution method used routinely in the laboratory involves pipetting 0.1 ml. of a 1:100 dilution of urine onto the surface of each agar plate. The 1:100 dilution of urine necessitates sequential ten-fold dilutions in two sterile dilution tubes containing physiological saline. The diluted urine is then streaked evenly over the surface of the agar plates with an ordinary bacteriologic loop. The cultures are incubated at 37° C. and the colonies counted after 24 hours. The number of colonies enumerated per plate, when multiplied by a factor of 1000, determines the number of bacteria in 1 ml. of the original urine.

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This paper was presented in part at the fall meeting of the Northwest Pediatric Society on September 27, 1963.

The loop method involves the streaking of a loopful of undiluted urine over the agar surfaces, followed by 24-hour incubation. Colony counts are performed in the same manner as the dilution method. The loop,* having an inner diameter of 1.45 mm. and consisting of platinum (96.5%) and rhodium (3.5%) wire of 0.0016 inch diameter, is calibrated by the manufacturer to deliver a 0.001 ml. volume of fluid. Because of this delivery volume, the number of colonies per plate × 1000 yields the number of colonies per ml. Round, sterile urine bottles several centimeters in diameter are desirable since they provide, after thorough mixing of the specimen, a large bubble-free surface of urine into which the loop may be dipped. Besides the calibrated loop and sterile urine bottles, other necessary equipment includes an incubator, a Bunsen burner and sterile agar plates.

TABLE 1

Comparison (Specimen by Specimen) of Tube Dilution (1:1000) and Calibrated Loop (0.001 ml) Quantitative Assay

Number of Specimens	Cols./ml by Tube Dilution Assay	Results of Calibrated Loop Assay	Per Cent Positive Correlation
60	$>10^5$	58, Identical 2, $10^4 - 10^5$	96.6
19	$10^4 - 10^5$	18, Identical 1, $>10^5$	94.7
56	$<10^4$	53, Identical 2, 10^4 1, $>10^5$	94.6

TABLE 2

Comparison of Tube Dilution Assay (Cols./ml) with Gram Smears of Uncentrifuged Urine

Cols./ml by Tube Dilution Assay	Number of Specimens	Gram Smear Negative	Gram Smear Positive*
$<10^4$	35	32	3
$10^4 - 10^5$	13	4	9
$>10^5$	47	1	46

*A positive gram smear consists of at least two (2) bacteria per 20 oil immersion fields.

Results

In a simultaneous comparison of 135 urine specimens, 60 yielded greater than 10^5 cols./ml. by the tube dilution method (Table 1). Fifty-eight of these 60 specimens (96.6%) were in the same quantitative category (cols./ml.) by the loop technique. Nineteen specimens contained between 10^4 and 10^5 cols./ml. by dilution technique, and 18 of these (94.7%) fell into an identical quantitative category by the loop method. Of the 56 specimens containing less than 10^4 cols./ml. by the tube dilution method, 53 (94.6%) were identical by the calibrated loop method.

Gram-stained smears of uncentrifuged urine were found to be generally accurate (Table 2). Observation of at least two microorganisms per 20 oil-immersion fields was required to establish a gram smear as positive. Thirty-two smears were negative out of 35 urine specimens (91.4%) containing less than 10^4 cols./ml. by the tube dilution method. Of 13 samples with colony counts between 10^4 and 10^5 per ml., nine (69.2%) had positive smears. The 47 urine specimens yielding greater than 10^5 cols./ml. had 46 (97.9%) positive gram smears.

Discussion

The classical tube dilution-pour plate technique for quantitative urine cultures was described by Sanford et al.[2] in 1956. It has been shown by Kass and others[3] that for clinical interpretation the quantitation of such cultures in colonies per ml. may be divided into three categories. Urine specimens containing greater than 10^5 cols./ml. constitute infection; counts between 10^4 and 10^5 cols./ml. indicate infection or contamination; and counts less than 10^4 cols./ml. usually result from cutaneous contamination.

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*Arthur H. Thomas Company, Catalogue No. 7433-C.

With simplified methods for bacteriologic quantitation of urine specimens, wide-spread patient survey in the clinic or office should be feasible. Quantitative studies would be extremely valuable from several standpoints. First, they provide a means for earlier diagnosis of insidious urinary tract infections. Second, evaluation of therapy would be significantly enhanced by frequent bacteriologic assay of active cases and prolonged follow-up cultures in "inactive" cases. Finally, data obtained from such studies should clarify our understanding of the incidence of urinary tract infections, their persistence, and their relationship to chronic or "healed" pyelonephritis. No one is in a better position to collect such data than the practitioner who may observe a patient population throughout many years, inclusive of initial therapy, intermittent laboratory evaluation, and, when necessary, necropsy study.

In this study, when compared to the tube dilution technique, the calibrated loop assay was approximately 95% accurate in the quantitation of uropathogens. Although the gram-stained smears of uncentrifuged urine were generally accurate, their sensitivity in the quantitative range of 10^4-10^5 cols./ml. was inferior to that of the loop method. Furthermore, the time required for inoculation, inspection, and interpretation of culture plates involved in the calibrated loop assay was found to be less than that required for preparation and microscopic examination of the gram smears. The loop technique offers the same advantage as the tube dilution-surface streak method in that positive cultures provide pure surface colonies which are often identifiable on the primary media after 24-hour incubation, or may easily be transferred to other media for further evaluation as well as for antimicrobial sensitivity studies. The majority of primary invaders can be identified on the original plates by an experienced observer without subculture. The most common uropathogen in the general population, Escherichia coli,[4,5,6] usually exhibits in colonial form an unmistakable green sheen on eosin-methylene blue agar plates. On the other hand, bacteriological screening based on microscopic examination of stained urine smears cannot provide the means for specific identification of the organism or evaluation of its sensitivity to antimicrobial agents.

Recent evaluation in our laboratory of two new methods for the quantitative culture of urine specimens, the triphenyltetrazolium chloride dye reduction test (Uroscreen*) and a paper strip-miniature rectangular agar plate assay (Uri-Tab**), have been found less suitable than the calibrated loop assay. Results of twenty-eight paired dye reduction tests and standard tube dilution assays correlated poorly, there being only 82% agreement. In addition, subculture of fluid from the Uroscreen tube would be necessary to retrieve and identify the infecting bacterium. Fifty-four similarly paired studies with the miniature agar plate assay revealed 82% agreement. The trypticase soy agar employed with the latter method would not allow simultaneous gross colonial indentification of the most common uropathogen, Escherichia coli.

Although the definitive diagnosis of many organisms and the evaluation of antimicrobial sensitivity of all organisms should be handled only by personnel skilled in bacteriological work, diagnostic screening and follow-up evaluation of therapy by quantitative urine culture is feasible for any small laboratory, including that of the practitioner's office, when the calibrated bacteriological loop is employed.

Summary

A simplified method for quantitative bacteriological culture of the urine employing a standard calibrated bacteriological loop is

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*Uroscreen, Knickerbocker Biologics, Pfizer Laboratories Division, Chas. Pfizer & Co., Inc.

**Uri-Tab, Dundee Laboratories, Inc.

accurate, yields pure bacterial colonies, and is well suited for widespread use in the office laboratory. The significant challenge of chronic pyelonephritis, its natural history and its eventuation from overt, subtle, or persistent urinary tract infection can be met by the practitioner in the office or clinic, using this tool for diagnosis and study.

This investigation was supported in part by a Public Health Service Fellowship (1-F2-HE-20, 664-01) from the National Heart Institute (Dr. Shaw).

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WHAT'S YOUR DIAGNOSIS?

A 56-year-old printer working at his press was stricken suddenly with severe anterior chest pain radiating into the left arm. The pain persisted for three hours, until he was admitted to the hospital and the pain relieved with morphine. There had been no previous illness.

Physical examination revealed a blood pressure of 120/80. Heart rate 80 and regular. The heart tones were normal and no murmurs were heard. The lungs were clear. There were no other abnormal physical findings. The white count was 15,000 with 86 per cent pmns. SGOT transaminase levels were 10, 60 and 40 units on three successive days. ECG showed a Q wave, elevated S-T and negative T wave in leads III and a Vf characteristic of a posterior myocardial infarction.

A diagnosis of a posterior myocardial infarction was made and the patient treated with anticoagulation and bed rest. During the first week he had a rise in temperature to 100, which returned to normal on the sixth day. On this day the patient complained of sudden increase of chest pain and stated that he felt very ill. His temperature rose to 104. Blood pressure was 80/60 and a grade IV harsh, low-pitched systolic murmur was audible at the apex and near the sternum, and in this area a systolic thrill was also apparent. There were rales in both lung bases. The patient was digitalized. His temperature returned to normal during the second week and remained normal thereafter. He lived 45 days, always in heart failure or on the verge of it. He was never free of heart failure and was found dead in bed 45 days after his hospitalization. What is your diagnosis? Turn to page 758.

A British scientist predicts that in time to come men will be born toothless. We thought, in our ignorance, that they usually were born that way. — Anon

Macroglobulins

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SINCE WALDENSTRÖM'S[1] description in 1944 of a series of patients whose serum contained markedly increased amounts of proteins with sedimentation constants in excess of 15 S20w, many techniques have been utilized by laboratories to increase the accuracy of identification and quantitation of these macroglobulins. Methods have included electrophoresis on a variety of media such as starch gel,[2] immunoelectrophoresis,[3] ultracentrifugation,[4] viscometry[5] and other immunochemical and physiochemical methods.[6]

The composition and structure of the three major groups of immunoglobulins, i.e., gamma-2 globulins, the gamma 1A globulins and the gamma 1M globulins, have been clarified by the work of Porter,[7] Cohen[8] and others. Immunologic methods have indicated the relation of macroglobulins in pathological states to normal serum globulins of the gamma 1M family.

This report concerns eight cases in which macroglobulins were found in increased amounts in the serum. They have been studied with paper and starch gel electrophoresis, immunoelectrophoresis, and ultracentrifugation techniques. Other simpler methods have also been employed. In addition, serum has been treated with penicillamine (ββ dimethylcysteine) to dissociate macroglobulins.[9]

Material and Methods

Eight sera containing pathological macroglobulins were examined. Of the eight patients studied, four had clinical evidence of primary macroglobulinemia. The remaining four had abnormal "M" bands on cellulose acetate or paper electrophoresis and rouleaux in the peripheral smear in conjunction with a mononuclear bone marrow infiltrate. Of the first seven cases, three presented with epistaxis, three with fatigue and weakness only, and one with pneumonia. These seven patients had varying combinations of hepatomegaly, splenomegaly and lymphadenopathy. The eighth patient is considered to be a case of lupus erythematosus.[4] All cases showed an excess of lymphocytes or abnormal mononuclear cells in the bone marrow as well as elevated sedimentation rates. None exhibited cryoglobulins. The amount of the macroglobulins found ranged from 680 mg./100 ml. to 3843 mg./100 ml. of serum. The S20w range was 14.9 to 17.16. All sera were separated from clotted blood immediately and stored at −5° C.

Total Serum Protein and Electrophoresis

Total serum protein was determined by the biuret method.[10] Paper electrophoresis was done with the Beckman Model "R" system. Bromphenol blue stained strips were scanned with a Model "RB" analytrol.

Starch Gel Electrophoresis

Vertical starch gel (11 %) electrophoresis[11] using Tris-borate 0.03M with respect to Tris, pH 8.02, for preparation of the gel and Borate Buffer 0.03M, pH 7.90 for the electrode compartment were utilized. Electrophoresis at 7 volts per cm. was continued for approximately four hours. Gels were sliced horizontally with a Buchler slicer and were stained with 1.14% Amidoschwarz 10B in a 5:1:5 water, acetic acid, methanol solution.

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Immunoelectrophoresis

Scheidegger's micromethod[12] with microscope slides was used. Two µl. serum was placed in a well in 1% agar in veronal buffer, pH 8.6, ionic strength 0.1 Separation was allowed to proceed for one hour at a 10V/cm. After filling the troughs with about 50 µl. of antiserum, diffusion was allowed to proceed for 20 hours. Unreacted proteins were washed out with 0.9% saline. This usually required 24 hours. Slides were dried, stained with Amidoschwarz 10B, and photographed.

Antisera

Polyvalent commercial horse antisera Lot 864-7 Immunology Inc., Chicago, Illinois, was used. Antigamma 1M(B2M) horse antisera lot 501-8 was obtained from Behringwerke, Frankfurt, (M) — Hoechst.

Penicillamine (ββ Dimethylcysteine) Treatment

A 100 µl. aliquot of whole serum to be tested was incubated with 25 µl. of a saturated solution of DL penicillamine in 0.85% saline for 12 hours at room temperature. A control specimen was incubated with saline only.

*Ultracentrifugation**

Ultracentrifugations were carried out at 59,780 r.p.m. (rev. min.) at 20° C. in a Spinco Model "E" machine with rotor temperature indicator control. Bar angles varied from 50° to 60°. Sera were diluted with 0.15 M NaCl. The usual corrections for temperature, density and viscosity using a $\overline{V}$ value of 0.73 were included in S20w calculations.

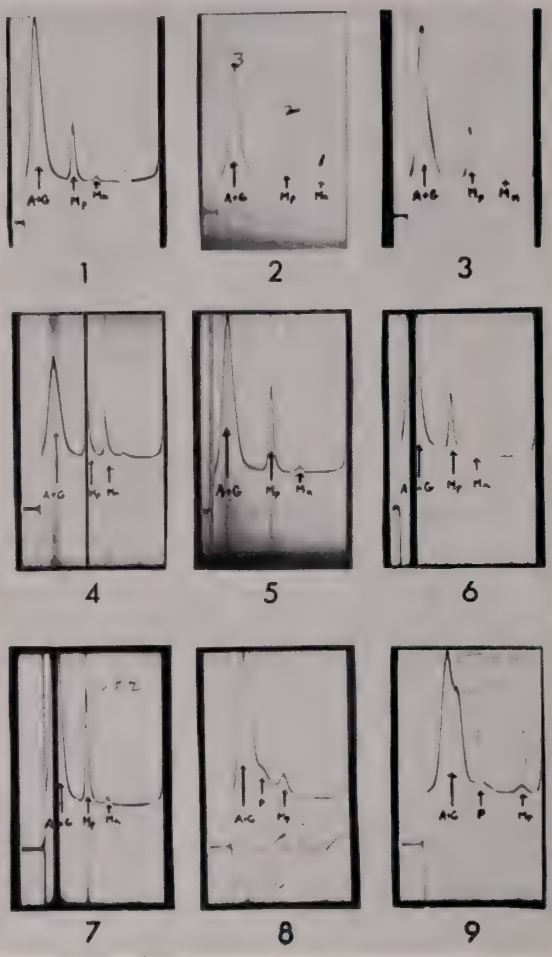

Fig. 1 — Ultracentrifuge Patterns.
1 to 8 — Cases 1 to 8
9 — later frame from Case 8
A + G = Albumin and globulin
Mp = Macroglobulin (S20w — 14.9 — 17.16)
Mn = Physiological macroglobulins (S20w — 20.90 — 27.6)
P = Protein (S20w — 9.47).

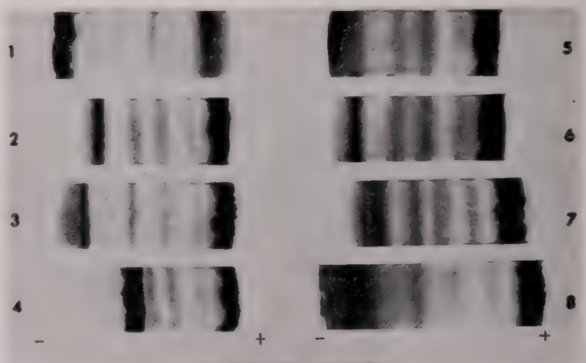

Fig. 2 — Paper Electrophoretic Patterns. Case 4 elevated protein is close to the beta band. All others are in the gamma range.

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*We wish to thank Doctor C. Kay, Department of Biochemistry, University of Alberta, who did the ultracentrifuge determinations.

The concentration of each component was determined from the area under its peak from the frame exhibiting the best separation of the component.[13] The method of counting squares was used to determine the relative amounts of individual components.

No correction was made for the Johnston-Ogston effect.

Results

Ultracentrifuge Analysis

Ultracentrifuge studies in all cases showed components in S20w range of 14.9 to 17.16 in amounts ranging from 8.19% to 42.7% of total protein (Figure 1). On the basis of total protein determination these ranged from 680 mg./100 ml. to 3843 mg./100 ml. of total protein (Table 1). These values were considered to confirm the presence of a macroglobulinemia. All but Case 8 have clinical, hematological, and bone-marrow findings consistent with macroglobulinemia. Case 8 was a female diagnosed as having disseminated lupus erythematosus who had a positive L.E. clot test and an additional protein with an S20w of 9.47 at a concentration of 3.2%. She will be the subject of a subsequent report but at this time has no other evidence of Waldenstrom's macroglobulinemia.

Routine Laboratory Procedures

In six of eight cases the total protein was below or within the normal range of 6.4 to 7.9 gm./100 ml. for our laboratory. In only two cases was there an elevation. The total globulin was elevated above our normal range of 2.5 to 3.6 gm./100 ml. in four of eight cases. Four were within normal limits (Table 2).

The Sia water test was positive at some time in the course of the disease in six cases, but this was not a consistent finding. Bence Jones proteins were found in only one case.

Paper Electrophoresis

Paper electrophoresis runs were not all of the same duration. They showed that all but Case 4 had the increased protein in the gamma globulin range. Case 4 showed the macroglobulin close to the beta globulin band. No pattern characteristic of macroglobulins was identified (Figure 2).

Starch Gel

On starch gel electrophoresis results were not uniform. Six cases stayed in or close to the point of application. Case 4 which was in the beta region on paper electrophoresis migrated toward the anode (Figure 3). In Case 8 the site of the macroglobulin could not be definitely identified. On dissociation with penicillamine Cases 1,3,5,7 showed movement toward the cathode. On careful inspection with transmitted light in Cases 3,5,7, these appear to consist of two bands. Cases 2

TABLE 1

Data on Ultracentrifugal Analysis

		Albumin		Globulin		Abnormal Macro Globulin		Macro Globulin		
Case	Dilution Pts. Serum Pts. NaCl (0.15M)	S20w	% Total	S20w	% Total	S20w	% Total	S20w	% Total	Abnormal Macro-globulin mg/100 ml.
1	1:4	3.79	70.0	6.29	18.0	14.90	12.0	21.40	1	708
2	1:6	4.28	81.3			17.16	16.4	25.49	2.3	969
3	1:5	4.19	79.0	6.0	5.4	16.30	15.4	24.00	0.2	955
4	1:9	4.20	43.3	6.7	3.5	14.90	42.7	20.90	8.9	3843
								27.60	1.6	
5	1:4	4.07	65.1	6.42	9.2	15.91	23.2	23.15	2.5	1018
6	1:5	4.04	83.4	6.37	2.2	15.49	13.4	22.78	1	849
7	1:5	4.09	73.7	6.66	5.2	15.31	19.8	22.63	1.3	1287
8	1:4	4.14	67.0	6.14	21.6	15.92	8.2			680
				9.47	3.2					

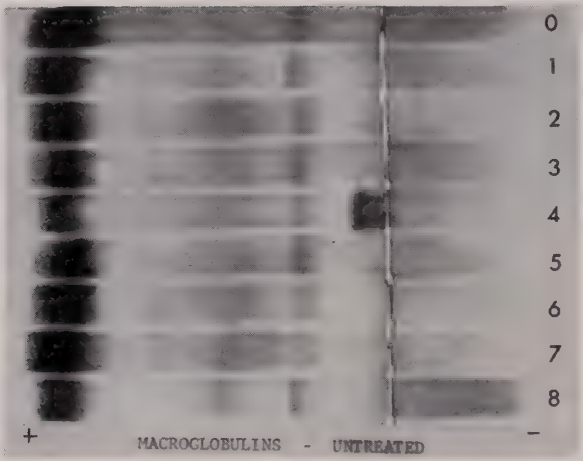

Fig. 3 — Starch Gel Electrophoresis of Whole Serum. 0 — is normal control serum. Case 4 exhibits anodal migration. Others are at or near the site of sample insertion.

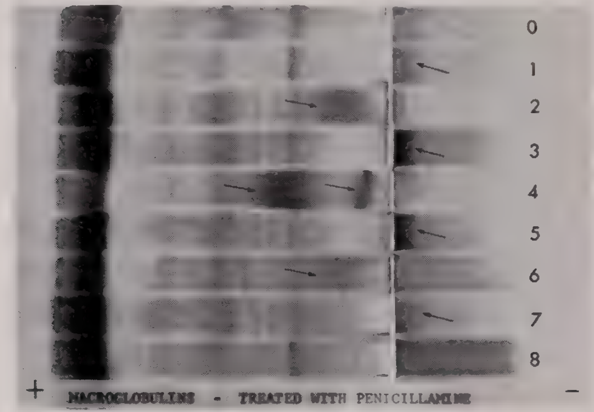

Fig. 4 — Starch Gel Electrophoresis — Penicillamine Treated. Whole serum. Strip numbers correspond to case numbers. Arrows show the site of the macroglobulin. The subdivisions as noted in the text are poorly seen in photographs.

and 6 showed four additional bands which had moved toward the anode in the beta region and which had not been seen in untreated specimens. Case 5 showed a large diffuse band which had moved anodally (Figure 4) and which on close inspection appeared to consist of four bands. A fifth band was present closer to the point of application. Case 8 showed no change with penicillamine treatment.

Immunoelectrophoresis

Using polyvalent antisera, a variety of patterns was seen (Figure 5). The macroglobulin remained at the well in Cases 1,3,8. In Case 2 an arc could be seen in the beta region. A diffuse band was seen in Case 5, but in others no abnormal arc was identified. In these cases no arc was seen at the usual gamma 1M site. When partially specific gamma 1M antisera was used on serum with and without penicillamine treatment the macroglobulin was identified in all cases. The site and shape of arcs was not uniform until the sera was treated with penicillamine. Penicillamine-treated sera showed a diffuse arc close to the trough in all cases (Figure 5).

Discussion

In this study of eight patients with abnormal amounts of macroglobulin, all but one (Case 8) had the evidence of macroglobulinemia of Waldenström. Total proteins or total globulins were not elevated in four patients and thus would not have indicated

TABLE 2

General Data

Case	Age	Sex	Hb. gm/100 ml.	W.B.C. c.mm.	Sed. Rate Win-trobe	Bence Jones Proteins In Urine	Total Proteins gm/100 ml.	Electrophoresis Total Globulin gm/100 ml.	Electrophoresis Gamma + M gm/100 ml.	Sia Test
1 (IA)	84	M	9.6	8300	43	-	5.9	3.8	1.6	+
2 (ED)	82	M	11.7	8700	44	-	5.9	2.6	1.3	+
3 (OF)	69	F	7.0	5500	63	-	6.2	2.8	1.7	+
4 (SG)	70	M	7.9	5500	47	-	9	6.9	5.7	-
5 (HS)	88	M	12.3	8000	57	+	6.4	3.9	2.1	+
6 (TW)	73	M	9.4	9300	66	-	6.3	3.5	1.5	+
7 (PP)		M	7.5	3400	72	-	6.5	3.3	1.7	-
8 (SS)*	45	F	14.6	2300	?	-	8.3	5.7	4.2	+

*Patient not admitted to this hospital.

the need for further study. The Sia Test was positive in six of eight cases at some time in the course of the study but was not positive in two of the cases, despite levels of macroglobulins in excess of 8% of the total protein. These procedures would, therefore, appear to be inadequate for screening techniques.

Paper electrophoresis in all cases showed the presence of an abnormality in the beta-gamma globulin range. Although the type of abnormality could not be defined, the technique appears to be an effective screening procedure.

In starch gel six of eight cases showed little penetration of the gel from the point of application. In one case a broad band of protein, taken to be the macroglobulin, migrated anodally. In the eighth case gamma globulin was increased but no conclusion could be reached as to the site of the macroglobulin. With penicillamine treatment results were also variable. In four instances migration toward the cathode occurred and in three of these two new bands were seen. The appearance of two bands which migrate toward the cathode in reduced specimens has been previously reported.[14,15] In three cases, after reduction, four additional bands were noted which had migrated toward the anode but in Case 8 no change was noted. Better separation of the additional bands could have been achieved at a lower pH.[15]

When whole serum is treated with penicillamine, immunoglobulins other than macroglobulins may be dissociated, and the appearance of additional bands may not be due to the presence of abnormal macroglobulins. Repolymerization may also be an influencing factor. The macroglobulins examined were heterogeneous, and confirmation of macroglobulins is difficult when starch gel electrophoresis is used.

Immunoelectrophoresis utilizing a broad spectrum antiserum was not entirely satisfactory. The site of the macroglobulin varied, and in three cases it could not definitely be identified. It was felt to be obscured by the gamma 2 arc. Macroglobulins in increased amounts were demonstrated in all eight cases by using a partially specific antiserum and penicillamine treatment.

With the anti gamma 1M antiserum the position of the macroglobulin was readily apparent. By pre-treating the serum with penicillamine a distinct spread curve appeared close to the trough in all cases.

It therefore appears that immunoelectrophoresis, utilizing these conditions, provides a satisfactory method of confirming the presence of macroglobulins in increased amounts.

Ultracentrifugation has been used to confirm the presence of macroglobulins in all cases. Seven of the cases are clinically, hematologically and biochemically compatible with primary macroglobulinemia. The eighth case has been clinically diagnosed as disseminated lupus erythematosus. The macroglobulin level is much higher than is usually

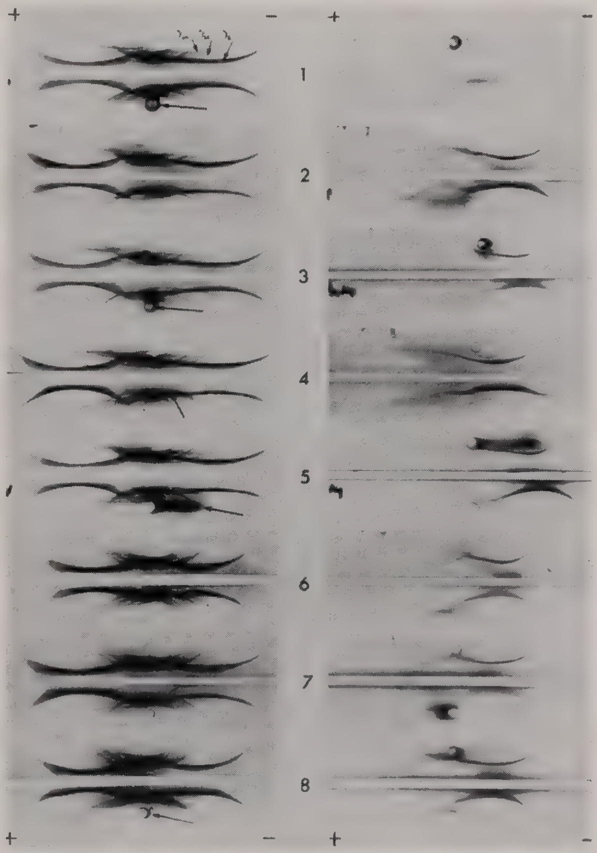

Fig. 5 — Immunoelectrophoretic Patterns. Each slide in the left column shows a normal control serum above and the patient's serum below, utilizing a broad spectrum antiserum. Macroglobulins are indicated with arrows. Each slide in the right column shows untreated patients' sera above and penicillamine-treated sera below using partially specific anti-gamma 1M anti-serum. A diffuse arc is noted in all penicillamine-treated sera.

noted in this disease. The diagnosis of primary macroglobulinemia on the basis of these protein studies should be made with caution and the possibility of secondary causes should be carefully considered.

Conclusion

A comparative study of the sera of eight patients which contained macroglobulins has been done using paper and starch gel electrophoresis, immunoelectrophoresis and ultracentrifugation as well as simpler procedures.

Total protein, total globulin and the Sia test were not effective as screening procedures. Paper electrophoresis showed that an abnormality was present in all cases.

Starch gel electrophoresis showed variable results which were difficult to interpret. Immunoelectrophoresis using partially specific gamma 1M antiserum, and penicillamine for dissociation, demonstrated the macroglobulin in all cases. Ultracentrifugation confirmed the presence of macroglobulins which had S20w's of 14.9 to 17.16 in amounts ranging from 8.19% to 42.7% of the total protein.

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ANSWER TO WHAT'S YOUR DIAGNOSIS

(From page 752)

Autopsy revealed infarction of the interventricular septum and posterior wall of the heart with a large septal perforation. When a systolic murmur develops during the course of a myocardial infarction the most common cause is a rupture of the interventricular septum. Other conditions to be thought of are rupture of a papillary muscle, a friction rub misinterpreted as a systolic murmur, mitral insufficiency or ventricular aneurysm. In this case cardiac catheterization was done in the fourth week, demonstrating a tremendous left to right shunt at the ventricular level, confirming the clinical impression of ruptured septum.

Gratitude

And a doctor has very much to be thankful for also. Don't you ever forget it. It is such a pleasure to do a little good that a man should pay for the privilege instead of being paid for it. Still, of course, he has his home to keep up, and his wife and children to support. But his patients are his friends — or they should be so. He goes from house to house, and his step and his voice are loved and welcomed in each. What could a man ask for more than that? And besides, he is forced to be a good man. It is impossible for him to be anything else. How can a man spend his whole life in seeing suffering bravely borne, and yet remain a hard or a vicious man? It is a noble, generous, kindly profession. — Sir Arthur Conan Doyle (1859-1930)

Whenever you see a man with handkerchief, socks, and tie to match, you may be sure he is wearing a present. — Frank Case

Blood Transfusion Problems in Auto-Immune Hemolytic Anemia

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FOLLOWING THE discovery of the antiglobulin reaction, Boorman et al.[1] established that some acquired hemolytic anemias show a positive direct antiglobulin reaction. Frequently the patients with auto-immune hemolytic anemia demonstrate an auto-antibody in the serum which agglutinates the erythrocytes of a large proportion of the blood donors tested.[2] For this reason, compatibility testing and transfusion of patients with auto-immune hemolytic anemia are very difficult.

The purpose of this article is to describe the serological investigations and compatibility testing of patients with auto-immune hemolytic anemia that is in current usage at the University of Minnesota Hospitals.

Clinical Material

Forty patients (23 females and 17 males) with positive Coombs tests and acquired hemolytic anemia were studied at the University of Minnesota Hospitals during a three-year period (1961-1964). All cases were referred to the Blood Bank for investigation of blood compatibility for transfusion.

Methods

The antibody in the serum was investigated for thermal reactivity by incubating 0.1 ml. of the patient's serum with 0.1 ml. of a 4% saline suspension of commercial test cells** at 4° C. and then at 37° C. for 60 minutes. This last incubation was followed by the antiglobulin reaction. A strong reaction at 4° C. indicated the presence of a cold antibody. In these cases, if the indirect Coombs test was found positive, the test was then repeated using washings with saline preheated at 37° C. before adding the antiglobulin serum. If the antibody was of the "cold type," the reaction was changed to negative or diminished considerably.

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**Hemantigen. Knickerbocker Biologics, Pfizer Labs. Div., New York, N. Y.

Preparation of Eluted Cells and Erythrocyte Eluates

If the antibody had maximum reactivity at 4° C., the blood samples were kept refrigerated at 4° C. and the serum separated before use. The cells were obtained by crushing the clot, followed by separation of red cells and washing several times (four to six times) in normal saline (1 volume of cells in 9 of saline) until the supernatant of the last saline washing appeared clear of free hemoglobin. Erythrocyte eluates were prepared by means of 56° C. treatment described by Landsteiner[3] with 2 ml. of packed erythrocytes in 0.8 ml. of normal saline for 5-10 minutes, care being taken to keep the centrifuge cups heated with warm water (56° C.). The eluted cells were then washed three times with normal saline and a 4% suspension was prepared. The same procedure was used when the antibody had a maximum reactivity at 37° C., but the blood samples were left at 25° C. for 1-2 hours before separation of serum and preparation of eluate and eluted cells.

Blood Grouping and Antiglobulin Tests

ABO and Rh blood grouping, direct and indirect antiglobulin tests were performed as described in the "Technical Methods and Procedures of the AABB."[4] Eluted and noneluted cells were used for ABO and Rh grouping as well for the investigation of the I antigen with anti-I in cases of auto-immune hemolytic anemia of the "cold antibody type."

Identification of Cold Auto-antibody

The antibody was studied by using 0.1 ml. of serum and 0.1 ml. of a 4% saline suspension of erythrocytes: Group O Rh negative adult erythrocytes, group O Rh negative cord erythrocytes, eluted patient's cells, noneluted patient's cells and a commercial panel of cells.* The mixtures were incubated at 4° C., 25° C. and 37° C. for 60 minutes. The presence of agglutination in all tubes containing the adult erythrocytes and absence in the tube with the cord erythrocytes in the mixtures incubated at 4° C. and/or 25° C. was indication of anti-I specificity. During the course of this study we found that the readings at 25° C. more critically differentiated the anti-I specificity. (These data are shown in Table 3). The presence of similar agglu-

TABLE 1

Forty Patients with Positive Coombs Hemolytic Anemia
with Crossmatch Problems
University of Minnesota Hospitals (1961-1964)

Primary or Idiopathic Auto-Immune Hemolytic Anemia	Cold antibody type			10
	Warm antibody type			7
Secondary or Symptomatic Auto-Immune Hemolytic Anemia	Cold antibody type	Lymphocytic malignancies	4	14
		Myeloproliferative diseases	3	
		Ca stomach	3	
		Multiple myeloma	1	
		Neuroblastoma	1	
		Burns	1	
		Infected wound	1	
	Warm antibody type	Systemic lupus erythematosus	2	9
		Lymphocytic malignancies	1	
		Myeloproliferative diseases	2	
		Hodgkins disease	1	
		Multiple myeloma	1	
		ITP (Evans' syndrome)	1	
		Aminoaciduria	1	

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*Knickerbocker Panocell, Knickerbocker Biologics, Pfizer Labs. Div., New York, N. Y.

tination in all tubes indicated the presence of a nonspecific cold auto-antibody.

Identification of "Warm Auto-antibody"

The eluates and sera were tested with eluted cells, noneluted cells and a commercial panel of cells, using the indirect antiglobulin reaction. The presence of positive agglutination with patient's eluted and/or noneluted cells indicated the "auto-antibody" nature of the antibody. The specificity or nonspecificity of the antibody was determined by the pattern of positive agglutination reactions obtained.

Compatibility Testing of Patients with Auto-immune Hemolytic Anemia

At least fifteen donors were tested for blood compatibility with each patient with auto-immune hemolytic anemia. All donors had ABO and Rh grouping which was identical with the patient's grouping. If the auto-antibody was warm, the standard compatibility testing as described by the American Association of Blood Banks[4] was used. When the antibody studied was of the warm non-specific variety, all the tests (crossmatches) gave positive results, and those positive results giving a weaker degree of agglutination were chosen for transfusion.

When the antibody was of the cold type (anti-I or nonspecific) the crossmatches were performed as described above with one modification; the washings were done with saline warmed previously at 37° C. before adding the antiglobulin reagent. All donors giving negative or weak reactions in the preceding tests were then investigated at room temperature for 60 minutes. The donors giving the weakest reactions were used for the transfusions.

Results

Thermal Reactivity of Auto-antibodies of Auto-Immune Hemolytic Anemia

As can be seen in Table 1, there were 24 patients with auto-immune hemolytic anemia of the "cold antibody type" and 16 with the "warm antibody type." The etiology of the forty cases with auto-immune hemolytic anemia may also be seen in Table 1. Seventeen of these cases were classified as idiopathic, the remaining 23 as secondary or symptomatic according to the primary disease of the patient.

Specificity of Auto-antibodies of Auto-Immune Hemolytic Anemia

Only 26 out of the 40 cases reported here were studied for specificity of the auto-anti-

TABLE 2

Specificity of Auto-Antibodies of Auto-Immune Hemolytic Anemia

				Total
Primary Auto-Immune Hemolytic Anemia	Cold antibody type	"Nonspecific"	3	
		Anti-I	2	5
	Warm antibody type	"Nonspecific"	5	
		Anti-e	1	
		Anti-E	1	7
Secondary Auto-Immune Hemolytic Anemia	Cold antibody type	"Nonspecific"	3	
		Anti-I	2	5
	Warm antibody type	"Nonspecific"	8	
		Anti-e	1	9

The specificity of the cold auto-antibodies was studied in the patients' sera and of the warm auto-antibodies in the eluates obtained from the patients' erythrocytes. The two auto-antibodies directed against the e antigen were established after absorption of the eluates with E/E erythrocytes to remove a nonspecific reactivity which reacted weakly with E/E erythrocytes.

bodies. As shown in Table 2, of the 10 cold antibodies studied, four showed anti-I specificity, and of the 16 warm antibodies, two showed anti-e specificity and one anti-E specificity. The apparent nonspecificity of six of 10 cases of cold antibodies could be, in part, due to the relative strength of the I antigen on the cord cells as revealed at 4° C. Table 3 shows a comparison of the reciprocal titers of cold agglutinins (anti-I) using adult and cord erythrocytes. It shows that the three examples of auto-anti-I studies showed strong reactions with both cord and adult erythrocytes when incubating the mixtures at 4° C. but not at 25° C., wherein the reactions are sharply different. The antibodies give negative reactions with cord erythrocytes at 25° C. and positive reactions with adult erythrocytes. The auto-anti-I with the lowest titer showed differences of reactivity at both 4° C. and 25° C. The detection of anti-I should be performed by incubation of cord and adult erythrocytes with patient's serum at both 4° C. and 25° C. and not at 4° C. only, as performed in the six cases where we found nonspecificity.

Discussion

The auto-antibodies of auto-immune hemolytic anemia are classified according to their thermal reactivity as "cold antibodies" or "warm antibodies." Warm antibodies have an optimum temperature for reactivity of about 37° C., are nonhemagglutinating and are detected by the antiglobulin reaction. They are highly avid for the red cell surface and therefore best studied in eluates obtained from the patient's own erythrocytes. Cold antibodies have an optimum temperature of reactivity at 4° C. and are detected by direct hemagglutination. They are found in high titer in the serum, because they are not avid for the erythrocyte surface, especially at 37° C. We have reported here the serological studies of 40 patients with Coombs-positive hemolytic anemia, who were referred to us because of difficulty in compatibility for blood transfusion. Twenty-four patients demonstrated cold auto-antibodies and 16 warm antibodies. Four out of 10 cold antibodies studied for specificity demonstrated anti-I specificity and three out of 16 warm antibodies demonstrated anti-Rh specificity of some kind. These patients with anti-Rh specificity can be transfused with compatible blood. The "nonspecific" auto-antibodies react with most blood donors, and for this reason, the patients, if transfused, receive incompatible blood. These nonspecific auto-antibodies show different degrees of reactivi-

TABLE 3

Comparison of Reciprocal Titers of Cold Agglutinins Using Adult and Cord Erythrocytes*

	4°C					25°C					37°C		
	Adult Group O Cells		Cord Group O Cells		i/i Cells	Adult Group O Cells		Cord Group O Cells		i/i Cells	Adult Group O Cells	Cord Group O Cells	i/i Cells
	Strength	Rec. titer	Strength	Rec. titer		Strength	Rec. titer	Strength	Rec. titer				
Auto-anti I													
A. H.	4+	2048	4+	512	0	3+	32	0	0	0	0	0	0
W. L.	4+	512	4+	124	0	2+	8	0	0	0	0	0	0
C. J.	4+	128	2+	32	0	+	Undil.	0	0	0	0	0	0
Iso-anti I													
F.	3+	16	+	2	0	+	Undil.	0	0	0	0	0	0

*The cold agglutinin titers were determined using 0.1 ml. of serial dilutions of the patient's serum and 0.1 ml. of a 4% saline suspension of erythrocytes of either Group O adult or cord blood. The mixtures were incubated for 60 minutes at 4°C., 25°C. and 37°C. The reciprocal of the last dilution which produced microscopic agglutination was recorded as the titer. The specificity of the cold agglutinin against I antigen was determined by the negative reactions obtained with i/i erythrocytes.

ties when tested with erythrocytes obtained from random donors. This is especially true when dealing with cold auto-antibodies.

An important contribution to the knowledge of auto-immune hemolytic anemia was made by Weiner et al.[5] when they described one case of auto-immune hemolytic anemia which yielded anti-e specificity in the eluate obtained from the patient's e/e erythrocytes. Since then several studies have pointed out frequent findings of warm auto-antibodies of hemolytic anemias directed to antigens of the Rh system — more frequently anti-e. Dacie[6] found in three sera that an apparently "nonspecific" antibody consisted of two components, one reacting with all cells tested and one reacting with all cells tested except -D-/-D-. W. Weiner extended these observations, demonstrating that 50 eluates from erythrocytes of patients with hemolytic anemia of the warm antibody type contain anti-Rh specificity of some kind.[7] They absorbed the eluates with Rh totally deleted (--/-- or dl), partially deleted (D--/D-- or pdl) and normal red cells (nl) and demonstrated three different specificities in the eluates directed against deleted, partially deleted and normal cells. In two examples of anti-e described by us in this article, the identification was possible after absorbing a nonspecific fraction with E/E erythrocytes before demonstrating two specificities: one versus the e antigen and one versus normal cells (nl).

Cold antibodies, on the other hand, have been known for several years to vary in the strength of their reactions with different cell samples from weak to very strong reactions. A. S. Wiener et al.[8] tested one serum of a patient with cold type antibody and described a new blood group system in 1956 — I blood group. The I negative individual i/i occurs about once in 20,000 donors. These persons have normally a "natural" anti-I. Auto-anti-I is usually found in people suffering from acquired hemolytic anemia of the cold antibody type, even though their eluted cells demonstrate the I antigen. Jenkins et al.[9] reported that cord cells gave relatively very weak reactions with powerful anti-I and failed to react at all with the less powerful anti-I. We found this to be true only when the reactions with cord and adult erythrocytes were carried out at 25°C. and not at 4°C. This partially explains the incidence of nonspecificity of cold antibodies which have been studied only at 4°C. At that temperature we have shown that the I antigen appears relatively strong in cord cells. In practice it is difficult to find donors i/i to transfuse patients with auto-anti-I. Transfusion of such patients and of patients with "nonspecific" warm auto-antibodies is indicated only as an emergency procedure to palliate severe symptoms of anemia-decompensation. With the procedures described here the patients are transfused with the donors which show the weakest degree of agglutination. It has been recommended[10] to transfuse the patient with 50 ml. of erythrocytes after obtaining a serum bilirubin and hemoglobin level. Four hours later determine the bilirubin again. A rise of bilirubin of less than .5 mg. is good evidence of not rapid erythrocyte destruction which allows the transfusion of the rest of the packed cells. Follow-up determinations of hemoglobin and bilirubin may give a better indication of benefit gained from the transfusion.

Summary

1. Forty patients with positive Coombs test and acquired hemolytic anemia were studied serologically and classified clinically according to the etiology of the hemolytic process. In seventeen cases no etiology could be determined to explain the hemolytic process; these were diagnosed as idiopathic auto-immune hemolytic anemia. The remaining twenty-three were symptomatic or secondary to the primary disease of the patient.

2. There were 24 patients with "cold antibody type" auto-immune hemolytic anemia and 16 patients with "warm antibody type" auto-immune hemolytic anemia.

3. The specificity of cold auto-antibodies was studied with the patients' sera and of warm auto-antibodies with eluates obtained from the patients' erythrocytes. Ten cold auto-antibodies were studied to determine anti-I specificity. In four cases the antibodies gave strong agglutination of adult

erythrocytes and negative reactions of cord erythrocytes following incubation at room temperature (25°C.) for 60 minutes and were classified as anti-I. Eluates obtained from the erythrocytes of 16 cases with warm antibody type were studied, showing specificity against the *e* antigen in two patients and against the E antigen in one case.

4. Transfusion of patients with autoimmune hemolytic anemia is always difficult because the crossmatches are regularly positive. We have described the procedures used in our laboratory to find the least incompatible blood for transfusion.

Acknowledgment

The authors wish to thank Miss Clareyse Nelson, Miss Sandra Benson, Mrs. Lila Wengler, Mrs. Betty Soderling, Mrs. Janet Svardal, Mrs. Mary Alice Grewe, Mrs. Kay Hager and Miss Jean Purcelli for their technical assistance.

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June 1966 Medical License Examination

At the February 11-12, 1966 meeting of this Board a request made by the President of the Senior Medical Class of the University of Minnesota Medical School was given consideration.

It was the determination of the Board that the request could be granted and the regular June 1966 examination (which would regularly be held June 21, 22 and 23, 1966) was re-scheduled for June 14, 15 and 16, 1966, in order to accommodate graduates who wish to leave for their internships.

Minnesota State Board of Medical Examiners
J. P. Medelman, M.D.
Secretary

The man who has not anything to boast of but his illustrious ancestors is like a potato — the only good belonging to him is underground. — Thomas Overbury

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The thumb takes the responsibility, the index finger the initiative. — Chazal

The Bedside Manner

Since the memory of man runneth not to the contrary the medical fraternity has been invested with its own distinctive mystique. Even the shaman had his aura!

Whence derives this indefinable, almost esoteric quality?

From its beginnings medicine developed its professional code and its *esprit de corps,* concurrently with its body and practice: a dual evolution much like that of English common law.

By Chaucer's time the doctors' deportment code was fairly well crystallized — as expounded by the trio of 14th century Johns: John of Gaddesden, John of Mirfield, and John of Arderne. A few provocative and illuminating gems, selected at random from that code, read as follows:

"Do not walk hastily, which betokens levity, or too slowly, which is a sign of faint-heartedness.

"When called to a patient, find out from his messenger as much about him as you can before you arrive. Then, if his pulse and urine tell you nothing, you can still surprise him with your knowledge of his condition.

"When feeling the patient's pulse, allow for the fact that he may be disturbed by your arrival and by the thought of the fee you are going to charge him.

"Hide your instruments from the sight of the patient — and from other doctors.

"Tell the patient that, with God's help, you hope to cure him, but inform the relatives that the case is grave. Then, if he dies, you will have safeguarded yourself. If he recovers, it will be a testimony to your skill and wisdom. When asked how long recovery will take, specify double the expected period. A quicker recovery will redound to your credit, whereas if a patient finds the cure taking longer than prophesied, he will lose faith in your skill. If he asks why the cure was so swift, tell him he was strong-hearted and had good healing flesh; he will then be proud and delighted.

"Do not sow dissension among the servants or offer them unsolicited advice, or brawl with anybody in the house.

"If you are asked to dinner, do not be over-effusive in your gratitude, and do not quibble about accepting the place of honour at the table. Be neither indiscreet nor exacting. Do not criticise the food, even if it is millet bread which turns your stomach. Stay sober. During the meal, enquire frequently after the patient, lest he suspect that you have forgotten him in your enjoyment of his viands.

"Tell the patient funny stories as well as recommending him to serious contemplations and to the Scriptures.

"If you do not wish to take on a case, pretend to be ill.

"If you find the patient dead on your arrival, show no surprise. Say you knew from the account of his symptoms he would not recover and enquire the hour at which he died. This will enhance your professional reputation.

"Missing from this list of instructions is the maxim which used to be quoted to medical students of a later day: 'The first thing to learn is not to kick the pot under the bed.' Also missing is the advice given by William of Salicet to the surgeon of the thirteenth century: 'A wise surgeon will refrain from stealing while he is in attendance on a patient.' "*

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*Turner, E. S.: Call the Doctor. St. Martin's Press, New York, 1959, p. 15-18.

Flagyl destroys trichomonads
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Flagyl eliminates the difficulties and frustrations that have long attended the treatment of trichomonal infection.

These difficulties arose mainly from:

1) the failure of any previously known agent to destroy the protozoan in paravaginal crypts and glands;

2) the failure of any previously known agent to prevent reinfection by eradicating the disease in male consorts.

The introduction of Flagyl removed both of these long-standing deficiencies. Hundreds of published investigations in thousands of patients have confirmed the ability of Flagyl to cure trichomoniasis.

Correctly used, with due attention to repeat courses of treatment for resistant, deep-seated invasion and to the presumption of reinfection from male consorts, Flagyl has repeatedly produced a cure rate of up to 100 per cent in large series of patients.

Nothing cures trichomoniasis like Flagyl.

Dosage and Administration

In *women:* one 250-mg. oral tablet t.i.d. for ten days. A vaginal insert of 500 mg. is available for local therapy when desired. When the inserts are used one vaginal insert should be placed high in the vaginal vault each day for ten days, and concurrently two oral tablets should be taken daily.

In *men:* in whom trichomonads have been demonstrated, one 250-mg. oral tablet b.i.d. for ten days.

Contraindications

Pregnancy; disease of the central nervous system; evidence or history of blood dyscrasia.

Precautions and Side Effects

Complete blood cell counts should be made before and after therapy, especially if a second course is necessary.

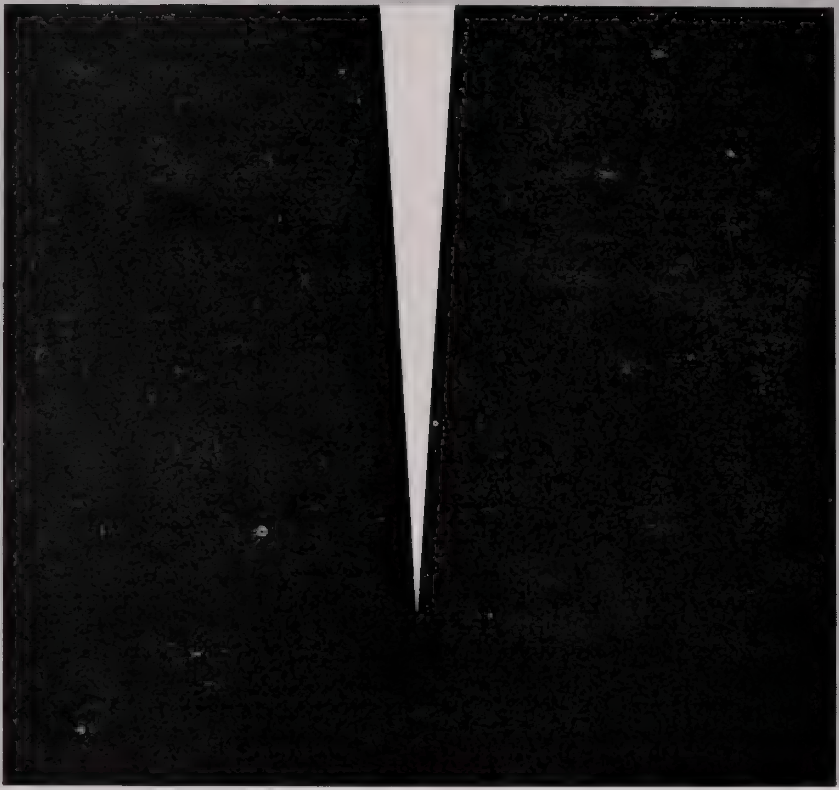
Infrequent and minor side effects include: nausea, unpleasant taste, furry tongue, headache, darkened urine, diarrhea, dizziness, dryness of mouth or vagina, skin rash, dysuria, depression, insomnia, edema. Elimination of trichomonads may aggravate moniliasis.

Dosage Forms

Oral–250-mg. tablets/Vaginal–500-mg. inserts

SEARLE

Research in the Service of Medicine



incisive

A good way to describe 'Stelazine'. It's different from the tranquilizers that sedate and dull your anxious patients. Its antianxiety effect is direct. On 'Stelazine', your patients can be calmed yet remain alert.

And 'Stelazine' offers additional benefits. Dependence has not been reported. At low doses, side effects are minimal. Its b.i.d. dosage is convenient and economical.

Stelazine®

brand of **trifluoperazine**

Indications: Symptoms of excessive anxiety. *Contraindicated* in comatose or greatly depressed states due to CNS depressants and in cases of existing blood dyscrasias, bone marrow depression and pre-existing liver damage. *Principal side effects,* usually dose related, may include mild skin reaction, dry mouth, insomnia, fatigue, drowsiness, dizziness and neuromuscular (extrapyramidal) reactions. Muscular weakness, anorexia, rash, lactation and blurred vision may also be observed. Blood dyscrasias and jaundice have been extremely rare. Use with caution in patients with impaired cardiovascular systems. Before prescribing, see SK&F product Prescribing Information.

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SK&F

Editorials

Gerald Taylor Evans, M.D., Ph.D.

THIS ISSUE OF MINNESOTA MEDICINE honors Gerald Taylor Evans, M.D., Ph.D., on the occasion of his twenty-fifth year at the University of Minnesota.

During the years since he came to Minnesota from Yale in 1939 Dr. Evans has made the University of Minnesota a leader in the field of Laboratory Medicine, viewed throughout the country as a foremost example of what can be accomplished in this field.

Gerald Taylor Evans was born March 11, 1900, in Galt, Ontario. After attending the University of British Columbia, he taught school in British Columbia before entering the McGill University Medical School in 1926. Following graduation, he continued graduate studies at McGill and the University of Pennsylvania, receiving the degree of Doctor of Philosophy from the latter institution in 1937. He was a member of the faculty in physiological chemistry at Yale University School of Medicine before coming to Minnesota as director of the clinical laboratory services in 1939. Under his leadership these services and their educational programs formed the Department of Laboratory Medicine in 1959, with Dr. Evans as Professor and Head of the new department.

This event was a momentous occasion. The department was the first Department of Laboratory Medicine in the United States, establishing a pattern of organization which is being repeated by other medical schools. The department is a monument to Dr. Evans' foresight and pioneering spirit.

On November 20 and 21, 1964, students and colleagues from all over the United States gathered in Minneapolis to honor Dr. and Mrs. Evans. A Silver Anniversary Symposium was held on those days. The program was made up of papers presented by colleagues and students. The original articles presented here originated from papers presented at the Evans' Symposium.

Gerald Evans has made many outstanding and lasting contributions to the medical school, to the state and to medicine in general. The most important of these lie in the following areas:

(1) The development of medical technology education.

(2) The development of high standards of clinical laboratory service.

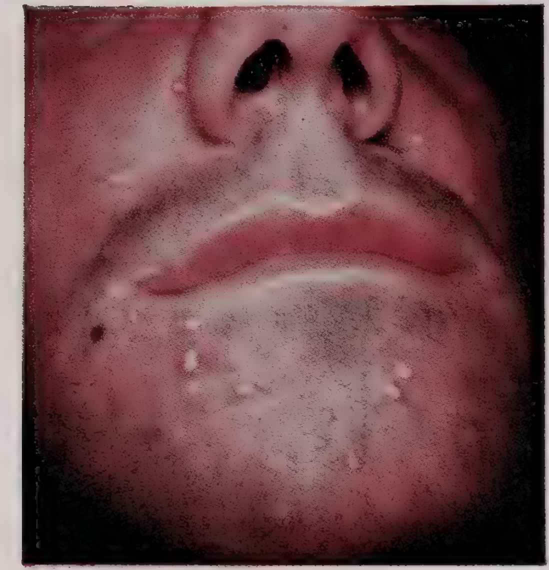
(3) Postgraduate education in clinical pathology.

(4) His strong influence on many young

Continued

TOPICAL TREATMENT

TYPICAL RESULTS



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'Aerosporin'® brand Polymyxin B Sulfate	5,000 Units
Zinc Bacitracin	400 Units
Neomycin Sulfate (equivalent to 3.5 mg. Neomycin Base)	5 mg.

Tubes of ½ oz. and 1 oz.

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Caution: As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms and/or fungi. Appropriate measures should be taken if this occurs.

Contraindication: This product is contraindicated in those individuals who have shown hypersensitivity to any of its components.

Complete literature available on request from Professional Services Dept. PML.

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people in medicine, inculcating a devotion to the highest ideals of medical practice, scholarship and science, has been and still is one of his greatest gifts.

When Gerald Evans came to Minnesota, he first undertook a strong pioneering development of an educational program in medical technology. Under his guidance, the course in medical technology at the University of Minnesota became generally considered the outstanding one in this country. Meticulous attention to high educational standards of technical excellence and professional ideals characterized this effort.

Next was undertaken the development of strong, versatile clinical laboratories in which careful attentiveness was directed especially toward quality of service. This effort was speeded forward by medical technologists, intelligent, able, with independent judgment, and schooled in the ideals of technical excellence and dedication to service which Dr. Evans had engendered.

Later, a sound program was established for the training of physicians in clinical pathology. This program accented graduate study through individual research and scholarship and exerted the same emphasis on intelligent attention to detail at the bench and on the wards, as have all of the efforts initiated by Dr. Evans.

Dr. Evans has always taken a vital interest in the teaching of medical students. The course in Laboratory Medicine in the sophomore year, a course which largely grew from his plans, emphasizes the use of the laboratory in the care of patients. The course, as he evolved it, is one which is closely related to clinical medicine: taking up laboratory topics and relating them to clinical situations in the diagnosis and care of patients. It illustrates well his concept of the supreme relevance of the laboratory to patient care, rather than a self-contained importance of the laboratory.

Gerry Evans has conceived of Laboratory Medicine as an island between the clinical fields and the basic medical sciences. Laboratory Medicine draws material and ideas from the basic sciences and makes them relevant to clinical medicine toward the goals of more perfect diagnosis and management of patients and, indeed, improvement and prolongation of human life.

He has been a kindly but firm and perceptive teacher and preceptor. Through his influence many young people have been motivated to seek goals they had not envisioned and to realize individual potentials of which they were not aware. Most of all, those who are proud to have been his students take pride in his imprimatur, an emphasis on quality of effort together with alert and informed sensitivity to the patient and his welfare.

Gerald Evans made several key decisions which were amazingly far-sighted in the formative years of Laboratory Medicine at Minnesota. Though his hand and mind were highly creative, he did not publish much of his thought and accomplishment. That which he did write was circularized to a few medical educators, hospital administrators and other colleagues and had immense impact on the course of developments at Minnesota and other institutions. Affectionately known as his Opus, it was written in 1959, and many of its passages are as cogent and predictive today as then. He has delineated in this "opus" a blueprint for the further development of Laboratory Medicine, pertinent not only to Minnesota but to other institutions as well.

Some words he wrote a few years ago concerning training in clinical pathology illustrate well the concepts which have guided his activities at Minnesota:

"We are in a technological revolution of an unprecedented nature. Our branch of the profession has the best intrinsic potential for measuring up to the new challenge in productive medicine.

"We are at the crossroads. Trade-vocational-apprenticeship type training is outmoded and should largely be abolished. Training should be planned, thorough, fundamental and flexible.

"Quality should be the lead objective. Although our trained members should have a broad viewpoint, they should not be generalists, professing comprehensive superficiality. Whether the individual is the pathologist, the

Continued

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Contraindications: Contraindicated in patients sensitive to sulfa or penicillin, pregnant females at term, premature infants, newborns during first week of life. **Precautions:** Watch for hypersensitivity reactions and overgrowth of nonsusceptible organisms. Observe usual precautions for sulfonamide therapy: adequate fluid intake; force fluids if urine volume is low; maintain urinary pH of 7 or higher; use only after critical appraisal in patients with liver or renal damage, urinary obstruction, blood dyscrasias. **Adverse Reactions:** Anaphylactoid shock (rare), G.I. disturbances, hepatitis, pancreatitis, blood dyscrasias, neuropathy, drug fever, urticaria, purpura, hematuria, crystalluria, conjunctival and scleral varicula, petechiae may occur. **Dosage:** Daily pediatric dosage should supply 65-100 mg. trisulfapyrimidines per pound body weight in divided doses q. 4 to 6 h. **Supply:** Pentid-Sulfas for Syrup when prepared, provides 80 cc. (16 doses) or 150 cc. (30 doses) of fruit-flavored syrup providing in each 5 cc. teaspoonful 125 mg. (200,000 u.) potassium penicillin G and 167 mg. each of sulfadiazine, sulfamethazine, and sulfamerazine.

Now . . . **NEW PENTID® '400'—SULFAS FOR SYRUP** (buffered penicillin powder with sulfadiazine, sulfamethazine, and sulfamerazine each 5 cc. providing 250 mg. [400,000 units] potassium penicillin G and 167 mg. each of sulfadiazine, sulfamethazine, and sulfamerazine). Available in 16-dose (80 cc.) and 30-dose (150 cc.) bottles.

For full information, see Product Brief.

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teacher or the highly specialized investigator (or all three), it is the *man* who should be trained and at a high level.

"There is an indivisibility of research, education and improved, even revolutionized, service."

Though these words were written concerning clinical pathology, they also pertain in many essentials to his thoughts about medical technology.

Gerald Evans has been a pioneer, a prophet, a planner, yes, even a dreamer, though many of his dreams will not come true for many years hence. Those who follow him at the University of Minnesota are immensely in his debt. He has set his department on a path which, if energetically and intelligently followed, will bring increasingly rich rewards to the University of Minnesota, to the state of Minnesota and to the professions which make up Laboratory Medicine as a whole.

Ellis S. Benson, M.D.*
Minneapolis, Minnesota

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*Professor, Laboratory Medicine, Director, Clinical Laboratories.

Laboratory Medicine — A Prospectus

THE CONTRIBUTION of the clinical laboratory to the diagnosis and management of patients has been accepted for many years. It therefore seems difficult to believe that the major growth of hospital laboratories has occurred during the past 25 years. Accordingly, it is appropriate to review several of the major trends which have developed during this recent period and to speculate on some of the developments which may be anticipated during the next 25 years. These developments will reflect improvements in scientific instrumentation, including advances in automation and data-processing techniques. Philosophically, they will recognize the increasingly important role of both outpatient and preventive medicine.

Specifically, what can be anticipated? Classically there are three major avenues of gathering information with reference to patient management: the history, the physical examination, and the laboratory examination. The roles of the history and the physical examination have become relatively well established. The role of the laboratory examination is rapidly changing, however, and may be expected to change even more dramatically in coming years. It is now accepted practice to gather historical information and physical findings concerning all of the major systems of the body at the time of a detailed clinical examination. It will soon be feasible to provide a similar laboratory examination which will reflect information regarding many of the major systems of the body. Such a battery of tests will be directly analagous to the current screening type of physical examination which provides information regarding heart, lungs, liver, etc. Laboratory examinations of this type will be performed at the time of hospital admission, as well as during periodic health examinations. Information gathered from such examinations will be recorded in a form facilitating retrieval and will be helpful in detecting asymptomatic pathology, in facilitating earlier diagnoses, and in shortening periods of hospitalization. Data will be considered not only on the basis of what is normal in the general population, but what may be considered normal for an individual of a specific age and sex. In addition, compilation of such information will facilitate establishing normal values for given individuals. Values which could be considered normal in reference to norms based on the general population may appear abnormal when considered in reference to a patient's own established "normal values."

In addition to laboratory screening batteries, clinicians will have new tests available which are of importance in the management of specific clinical problems. Many of these tests will not be of general value and hence will not be incorporated in screening batter-

Continued

An antibiotic of choice is one that works

TAO works

Susceptibility Results
Staphylococci [2,3,1]

# OF CULTURES	YEAR	% EFFECTIVE
6,725	1962	88.6%
5,440	1963	88.0%
10,384	1964	88.5%

β-Hemolytic Streptococci [2,3,1]

# OF CULTURES	YEAR	% EFFECTIVE
2,448	1962	89.5%
1,519	1963	95.2%
2,492	1964	96.7%

The Product

In a world study of antibiotics ***in vitro***[1], TAO had an overall effectiveness of 87.3%, higher than chloramphenicol and erythromycin, and significantly higher than tetracycline and penicillin.

The Plus... Consistent Performance

Yet antibiotics must not only work. They must work consistently. Here are the results from the largest study of microbial susceptibility ever undertaken. In 29,048 cultures of overt staphylococcal and β-hemolytic streptococcal infections, note the consistency of results with TAO.

TAO®

[triacetyloleandomycin]

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TAO Rx information

Indications: The bacterial spectrum includes: streptococci, staphylocci, pneumococci and gonococci. Recommended for acute, severe infections where adequate sensitivity testing has demonstrated susceptibility to this antibiotic and resistance to less toxic agents. **Contraindications and Precautions**: TAO (triacetyloleandomycin) is not recommended for prophylaxis or in the treatment of infectious processes which may require more than ten days continuous therapy. In view of the possible hepatotoxicity of this drug when therapy beyond ten days proves necessary, other less toxic agents, of course, should be used. If clinical judgement dictates continuation of therapy for longer periods, serial monitoring of liver profile is recommended, and the drug should be discontinued at the first evidence of any form of liver abnormality. It is contraindicated in pre-existing liver disease or dysfunction, and in individuals who have shown hypersensitivity to the drug. Although reactions of an allergic nature are infrequent and seldom severe, those of the anaphylactoid type have occurred on rare occasions. **References**: 1. Isenberg, Henry D.: Health Laboratory Science **2**:163-173 (July) 1965. 2. Fowler, J. Ralph et al: Clinical Medicine **70**:547 (Mar.) 1963. 3. Isenberg, Henry D.: Health Laboratory Science **1**:185-256 (July-Aug.) 1964.

ies. For particular patients with particular pathologies such tests will be invaluable, however, and accordingly, the number of investigations performed by clinical laboratories will continue to increase.

Laboratory growth is accelerating and, in response to the clinicians' requests, the number of determinations performed in hospital laboratories is currently increasing at a rate of 10-30% annually. As would be expected, the trends discussed above are already in progress. Automation in the clinical laboratory, systems of data retrieval, computer techniques, and new analytic methods are currently the subjects of numerous national and international meetings and symposia. On the basis of these developments one may predict that clinicians will receive increasingly better support from clinical laboratories during the next 25 years. If one considers these current trends in laboratory medicine in conjunction with the advances which may be anticipated in other diagnostic methods and in therapeutic techniques, accelerated improvement in patient care appears inevitable.

Paul E. Strandjord, M.D.*
Minneapolis, Minnesota

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*Assistant Professor, Director, Clinical Chemistry Division.

The Future of Medical Technology

DOES MEDICAL TECHNOLOGY as a separate professional entity have a future or will it be absorbed and replaced by specialists in laboratory medicine?

From a practical standpoint Medical Technology must continue to exist as a separate professional entity because physicians and hospitals require versatility in technological skills. The usual volume of demands does not warrant specialists. Another practical consideration is that in hospitals technologists must be available for emergencies, and involving several people in this emergency activity becomes economically prohibitive.

Practical expediency, however, cannot be the basis for the existence of a profession. If Medical Technologists did not exist, solutions would be found to practical problems, primarily by the substitutions of nonprofessional personnel trained in a few techniques or by joint utilization of facilities and personnel between neighboring institutions. The consequences of this kind of limited laboratory service to patient care could be disastrous. The unique resource of the profession needs evaluation and definition. How does a Medical Technologist differ from a technician in the laboratory? A technician knows how to perform certain techniques but a technologist also knows why. The technologist is trained to think and to apply principles, even when confronted with an unfamiliar test.

With the increasing variety and complexity of laboratory determinations the profession of Medical Technology must modify its training and its operation towards increased application of basic knowledge rather than increased technical maneuvers. The correlation of basic chemical and biological principles to clinical application must be emphasized. Less time should be devoted to so-called "bench" training and more time to guided investigation of application of principles in established methods and in new procedures. Medical Technology can offer something unique to patient care, viz., the individual who has the basic knowledge in all laboratory fields and who can apply this knowledge to new situations and demands. The future is broad for Medical Technology; but only a self-inflicted amputation from tradition and a complete prosthesis can realize that future.

Verna Rausch, M.S., M.T. (ASCP)*
Minneapolis, Minnesota

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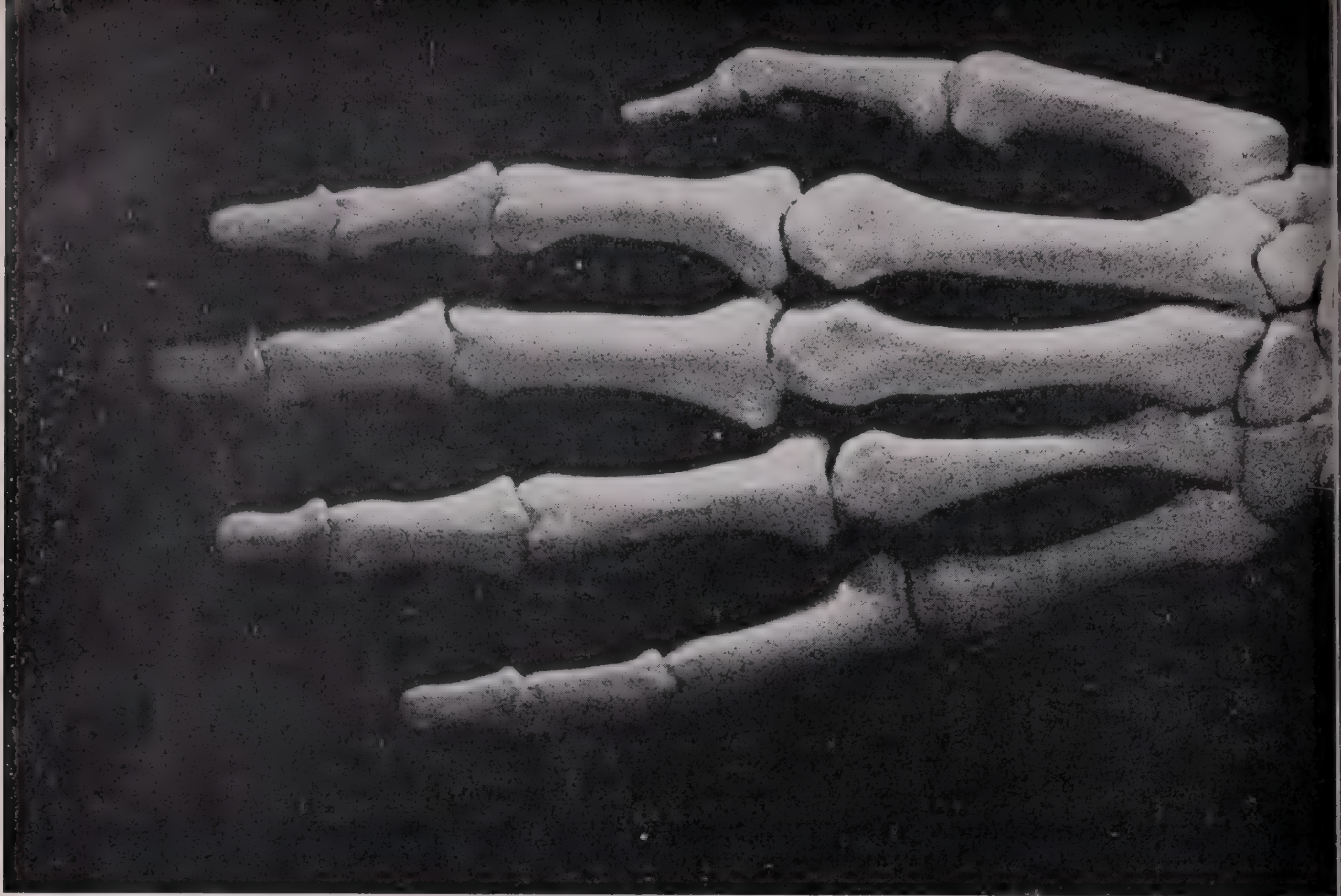
*Associate Professor and Training Coordinator, Division of Medical Technology.



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phenylbutazone	100 mg.
dried aluminum hydroxide gel	100 mg.
magnesium trisilicate	150 mg.
homatropine methylbromide	1.25 mg.

In rheumatoid arthritis–effective thera
with minimal chance of G-I upset

Therapeutic Effects
Fifty to 75% of patients obtain major relief of arthritic symptoms, as reported by numerous clinicians. In addition, the problem of gastric upset—a major problem with certain other oral antiarthritic agents—is minimized by the presence of antacids and an antispasmodic in the formulation.

Improvement is generally seen within 3 to 4 days, and trial therapy need not be continued beyond a week. Relief of pain is followed quickly by resolution of inflammation and improved joint function. Relief of symptoms is often accompanied by increased appetite, gain in weight and an improved sense of well-being.

The initial response is usually maintained without dosage increases; indeed, initial dosage is often reduced for maintenance purposes.

Salicylate or steroid therapy can usually be diminished or, in some instances, eliminated.

Contraindications
Edema; danger of cardiac decompensation; history or symptoms of peptic ulcer; renal, hepatic or cardiac damage; history of drug allergy; history of blood dyscrasia. Because of the increased possibility of toxic reactions, the drug should not be given when the patient is senile or when other potent chemotherapeutic agents are given concurrently. Large doses of Butazolidin alka are contraindicated in patients with glaucoma.

Precautions
Before prescribing, the physician should obtain a detailed history and perform a complete physical and laboratory examination, including a blood count. The patient should be kept under close supervision and should be warned to report immediately fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools. Regular blood counts should be made. The drug should be used with greater care in the elderly.

Warning
If coumarin-type anticoagulants are given simultaneously, the physician should watch for excessive increase in prothrombin time.

Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea and sulfonamide-type agents and insulin. Patients receiving such concomitant therapy should be carefully observed for this effect.

Adverse Reactions
The most common adverse reactions are nausea, edema and drug rash. The drug may reactivate a latent peptic ulcer. Infrequently, agranulocytosis, generalized allergic reaction, stomatitis, salivary gland enlargement, vertigo and languor may
occur. Leukemia and leukemoid react
have been reported but cannot definit
attributed to the drug. Thrombocytope
purpura and aplastic anemia are also
sible side effects. Confusional states,
agitation, headache, blurred vision, op
neuritis and transient hearing loss hav
been reported, as have hepatitis, jaun
and several cases of anuria and hemat
With long-term use, reversible thyroid
hyperplasia may occur infrequently.

Average Dosage in Rheumatoid Arthri
Initial: 3 to 6 capsules daily in divided
It is usually unnecessary to exceed 4 c
sules daily. A trial period of 1 week is a
quate to determine response; in the ab
of favorable response, discontinue.

Maintenance: An effective level is ofte
achieved with 1 to 2 capsules daily; do
exceed 4 daily.

Also available:
Butazolidin®, phenylbutazone
Tablets of 100 mg.

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The Uncertain Year of 1916

THE FOREBODING year of 1916 was indeed one to remember. Early in March, Pancho Villa and his boisterous guerillas raided Columbus, New Mexico, and were pursued by an American brigadier general then almost wholly unknown to the public — John J. Pershing. Lord Kitchener of Khartoum, Britain's hope for leadership in World War I, in June was drowned at sea on his way to Russia on a military mission. Sir Roger Casement, the quixotic Irish patriot, was hanged in London in August; after an exciting election evening in November, Mr. Justice Charles Evans Hughes went to bed, and his confident aides told inquiring newspapermen: "The President has retired for the night." The next morning, however, Mr. Hughes discovered that Woodrow Wilson was the President and that he was not. Nearly everyone sensed that America would go to war, but very few found any pleasure in the premonition.

The best-selling new novels of 1916 were *Tish,* by Mary Roberts Rinehart; and *Penrod and Sam,* by Booth Tarkington. On the stage Ethel Barrymore was a great success as the lady drummer in Edna Ferber's "Our Mrs. McChesney," and the male idol of the moment was William Faversham in George Bernard Shaw's "Getting Married." In American homes pianos were banging out "K-K-Katy, Beautiful Katy," and "Tipperary," and William Farnum and Mary Miles Minter were the reigning peers of an infant motion-picture industry. Elsie Janis and Sir Harry Lauder were supreme on the vaudeville stage.

It has been my privilege to know intimately two of the men who were graduated in medicine in 1916 and who thus became members this year of the "Fifty Club" of the Minnesota State Medical Association. One is Dr. Harry LeRoy Smith and the other is Dr. Austin C. Davis, both internists, both my colleagues and both members of the same class in the State University of Iowa College of Medicine. Both were superlatively fine practitioners, gifted with perceptive intuition, superior clinical judgment and the rare capacity for long hours of hard work and the stamina to sustain them.

Dr. Davis in 1916 was an intern in the State University of Iowa Hospitals. He followed the course of most young medical graduates of that era by going into the Army Medical Corps in 1917; then he returned to his university to lecture on medicine until 1923, when he was appointed a first assistant in medicine in the Mayo Clinic. He became a member of the staff of the Mayo Clinic and remained so until his retirement on October 1, 1956. At that time he had attained the rank of assistant professor of medicine in the Mayo Graduate School of Medicine, and since that time he has lived in Pompano Beach, Florida.

It is fortunate for most of us that men like Austin Davis do not come along very often, for in this instance emulation would be difficult indeed or, what is nearer the truth, impossible of success. His keen intellect and profound discernment were accompanied by a quiet humor and an unfailing gentleness of nature; he was never obtrusive and was ever courteous, yet he had within him an abundance of natural gifts which a lesser man would have exploited with an aggressiveness and an indifference to others abhorrent to Austin Davis and alien to his character.

Dr. H. L. Smith, graduating in medicine with Austin Davis in 1916 at the State University of Iowa, was an intern at the Vancouver General Hospital until November, 1917, when he, too, entered the Army Medical Corps for service in France. His war experiences he narrated vividly in 1940 in his book, *Memoirs of an Ambulance Company Officer.* They show that wherever the fighting was, there also was Roy Smith. He returned to Walnut, Iowa, where until 1925 he carried on the vastly instructive and personally satisfying practice of a small-town physician. Then he came to Rochester as a fellow in medicine of the Mayo Graduate School of Medicine; he was appointed to the staff of the Mayo Clinic in 1928 and continued as such until October 1, 1952, when he retired. At that time he was professor of medicine in the Mayo Graduate School of Medicine.

Roy Smith was known to his intimates as

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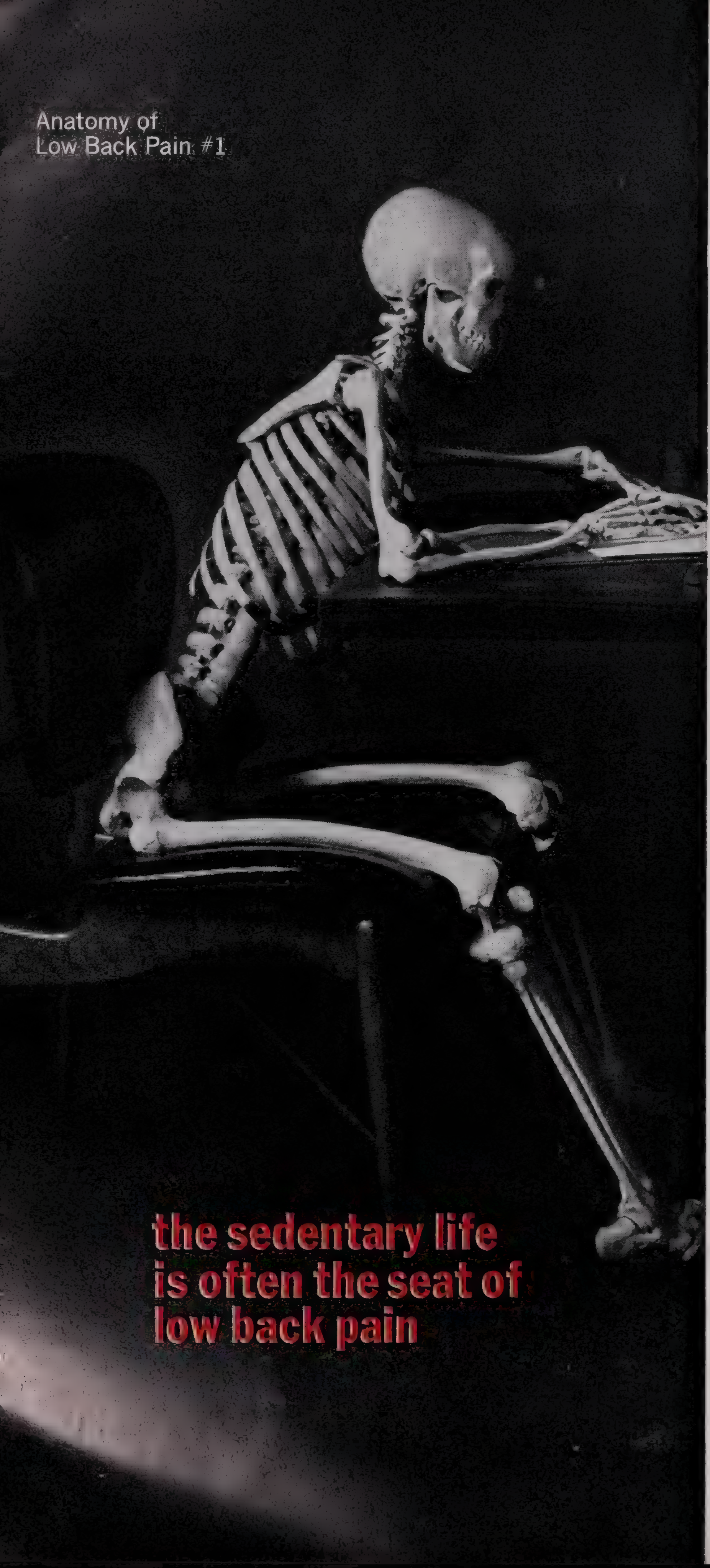

The human spine is not engineered f prolonged sitting at desks, pianos, typ writers and drafting boards. The stress set up by the heavy, forward-tilted hea and trunk, balanced precariously on a insufficient base, result in strain of th dorsal musculature, particularly at th low lumbar level.

The unusual muscle-relaxant and ana gesic properties of 'Soma' make it esp cially useful in the treatment of low bac sprains and strains. 'Soma' is wide prescribed ☐ **to relieve pain** ☐ **to rela muscles** ☐ **to restore mobility.**

Indications: 'Soma' is useful for management muscle spasm, pain, and stiffness in a variety inflammatory, traumatic, and degenerative musc loskeletal conditions. It also may act to normali motor activity in certain neurologic disturbance

Contraindications: Allergic or idiosyncratic rea tions to carisoprodol.

Precautions: 'Soma', like other central nervo system depressants, should be used with cauti in patients with known propensity for taking e cessive quantities of drugs and in patients wi known sensitivity to compounds of similar chem cal structure, e.g., meprobamate.

Side Effects: The only side effect reported with a frequency is sleepiness, usually on higher tha recommended doses. An occasional patient m not tolerate carisoprodol because of an individu reaction, such as a sensation of weakness. Oth rarely observed reactions have included dizzines ataxia, tremor, agitation, irritability, headache, i crease in eosinophil count, flushing of face, a gastrointestinal symptoms.

One instance each of pancytopenia and leuk penia, occurring when carisoprodol was admi istered with other drugs, has been reported, as h an instance of fixed drug eruption with carisoprod and subsequent cross reaction to meprobamat Rare allergic reactions, usually mild, have includ one case each of anaphylactoid reaction with mi shock and angioneurotic edema with respirato difficulty, both reversed with appropriate therap In cases of allergic or hypersensitivity reactior carisoprodol should be discontinued and approp ate therapy initiated. Suicidal attempts may pr duce coma and/or mild shock and respirato depression.

Dosage: Usual adult dose is one 350 mg. tabl three times daily and at bedtime.

Supplied: Two Strengths: 350 mg. white table and 250 mg. orange, two-piece capsules.

Before prescribing, consult package circular.

for the relief of low back sprains and strain

SOMA
(CARISOPRODOL

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26501

a fellow of sharp wit and abundant humor which, however, were invariably cloaked beneath the impassive countenance of an upright deacon. His expressionless face, at a moment of some pungent jest or sally, made his japery the more effective because it always took the recipient by surprise. Like Austin Davis, he was the accomplished internist, never swayed by the vagaries of the latest therapeutic enthusiasm, properly suspicious of the virtues of the newest curative agents introduced with much fanfare and sounding brass, penetrating in his diagnostic acumen and admirable in his ministrations. It is characteristic of his sound spirit of inquiry that his master's thesis of 1928, on the relation of the weight of the heart to the body and to age, has come to be a widely used guide to the weight of the normal heart. In 1953 Roy Smith became the publisher of an ancient pre-Civil War weekly newspaper, *The Mantorville Express,* where, for 52 issues, both his irrepressible wit and his innate common sense were unmistakably evident in always judicious measure. Since his retirement he has continued to live in Rochester.

Frank J. Heck, M.D.*
Rochester, Minnesota

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*Mayo Clinic and Mayo Foundation: Emeritus Consultant, Section of Medicine.

Test Your Word Score

Satellitosis — *accumulation of glia cells about the ganglion cells of the brain cortex* (page 736).

Keratopathy — *lesions affecting the cornea — diseases attended by horny growths* (page 737).

Paradoxical — *seeming to be contradictory* (page 740).

Helical — *in the form of a spiral* (page 746).

Kernicterus — *a grave form of icterus neonatorium with generative lesions in portions of the brain* (page 804).

Anamnestic — *assisting the memory* (page 811).

Pica — *hunger for substances not fit for food* (page 818).

Thallium — *a metallic element of the aluminum family — with actively poisonous salts* (page 819).

Poikilocytosis — *a condition in which abnormal erythrocytes appear in the blood* (page 821).

Acanthrocytosis — *a rare condition in which as many as 70 to 80 per cent of the red blood cells are spherocytes with pseudopod-like projections, with increased fragility and lipolethicin content. (The condition is thought to result from a mutant recessive allele.)* (page 821).

Letter to the Editor:

Enclosed you will find the letter we were talking about. The letter was sent to my daughter, Alice, at Macalester College when she was a freshman. It was with a great deal of satisfaction that I was advised that the poem was put on the bulletin board at her dormitory.

Karl W. Anderson, M.D.
Senior Vice President and Medical Director
Northwestern National Life Insurance Company

BE A MYTH-MONGER #1

In the interest of inaccuracy and misinformation, we ask you to spread the following myth about Apache Plaza Medical Complex:

APACHE PLAZA MEDICAL COMPLEX IS TOO EXPENSIVE.

To be completely fair, some doctors think that's *not* a myth. For half the cost they can rent space above a beer joint in a run-down neighborhood. But, for the doctor who buys top-flight equipment, hires first-rate help, and avoids buying used cars because he doesn't want to take on someone else's problems . . . for that doctor, Apache Plaza Medical Complex makes sense. And it isn't expensive. It's just first class.

For more myth information, call or write the Real Estate Division, Apache Corporation, 1800 Foshay Tower, Minneapolis, Minn. 55402. Telephone: (612) 339-7781.

APACHE PLAZA MEDICAL COMPLEX

Stinson Boulevard at 40th Ave., N.E.
St. Anthony Village, Minnesota 55421

BE A MYTH-MONGER #2

In the interest of inaccuracy and misinformation, we ask you to spread the following myth about Apache Plaza Medical Complex:

YOUR PATIENTS WON'T FOLLOW YOU TO A NEW MEDICAL BUILDING NEAR A SHOPPING CENTER.

Funny. That's what people told us when we built Apache Plaza in the first place. "People won't come all the way out here to shop." But they do—some from the other side of Minneapolis. Patients will follow the *good* doctor—wherever he goes.

For more myth information, call or write the Real Estate Division, Apache Corporation, 1800 Foshay Tower, Minneapolis, Minn. 55402. Telephone: (612) 339-7781.

APACHE PLAZA MEDICAL COMPLEX

Stinson Boulevard at 40th Ave., N.E.
St. Anthony Village, Minnesota 55421

My dear Alice:

I just came upon a poem that I think is apropos that a father should send to his daughter who has just started college. I hope you not only enjoy reading the poem but that you take it to heart. I send this poem to you and finish the letter using the three greatest words in the English language.

I Love You, (Signed Father)

Lines to a Daughter

by Agnes Rogers

One of the things that you really should know
Is when to say "yes," and when to say "no."
It's terribly, terribly risky to guess
At when to say "no" and when to say "yes."
Girls who are slaving for Woolworth and Kress
Lament for the day when they might have said "yes,"
Others are crying at night apropos
Of moments when clearly they should have said "no."
There aren't any textbooks, there aren't many rules,
The subject's neglected in orthodox schools.
Experience helps, but you seldom remember
Your April mistakes by the first of November.
You can't be consistent; there's often a reason
For changing your mind with a change in the season.
You may be quite right in accepting at seven
Suggestions you'd better refuse at eleven.
Perhaps you'll consider these tentative hints:
"No" to a dirndl of highly glazed chintz,
"Yes" to the bashful young man at the dance,
"No" to the man who's been living in France,
"Yes" to a walk in the park in the rain,
"Yes" if he asks for a chance to explain,
"No" to all slacks unless you're too thin,
"No" to that impulse to telephone him,
"Yes" to a baby, and "no" to a bore,
"No" if you're asked if you've heard it before,
"Yes" to the friend when she says, "Don't you think
Rabbit is just as becoming as mink?"
"Yes" to a Saturday, "no" to a Monday,
"Yes" to a salad and "no" to a sundae,
"No" to a wastrel and "yes" to a ranger,
"No" to a toady, and "yes" to a stranger
(That is, providing you use some discretion),
"No" to three cocktails in rapid succession,
"No" to magenta and chocolate brown,
"Yes" to a whisper and "no" to a frown,
"No" if he's misunderstood by his wife,
"Yes" if you want it the rest of your life.
Remember, my darling, careers and caresses
Depend on our choices of "noes" and of "yesses."

the mid-rift!

Our population's bursting at the seams.

It's eat. Eat. Eat.

And then diet. Diet. Diet.

With the latest No-calorie.
No carbohydrate. No-vitamin. No exercise.
400-hour Kamikaze Plan!

When it's over, it's eat, eat, eat again.

As a professional you can help wrest some sense from this nonsense: first, by cautioning against skipping meals, and second by pointing the way to realistic weight control through nourishing meals every day. Day after day.

Naturally, balanced diets and nourishing, palatable dairy foods go together; they always have.

Project Weight Watch has been initiated to assist you. Its scope is nationwide, its purpose is to focus professional attention on the problem.

To help you translate your concern to your patients, a portfolio of materials is available. Send for it. Help stamp out needless waist.

Dairy Council of the Twin Cities
1550 W. Larpenteur Avenue
St. Paul, Minnesota 55102

Dear Dietitian:
Please send me your free portfolio of Weight Watch materials.

Name____________________
Address__________________
City__________ State______ Zip Code______

Servicing the Greater Twin City Metropolitan Area

PROJECT WEIGHT WATCH

The Editor's Soliloquy

Obfuscuity

"If language is not correct, then what is said is not what is meant; if what is said is not what is meant, then what ought to be remains undone." Confucius

Obscurantism diffuses like a fog through medical writing. The message of this essay is that obscurity, when properly used, can lead to publication. The obscurantist's goal is clear — to produce the greatest number of papers from the minimal amount of data using the maximal number of words.

The code is straightforward: to say nothing well and not to stop when you have said it. The obscurist believes that clarity is degrading, that blunt statements are impolite, and that vagueness is safer than precision. Although the code is simple, the gambits require definition. There are three basic ploys for physicians who aspire to turbid, but publishable, prose.

Windfoggery is the bedrock of all abstruseness. Wind and fog do not coexist in nature but merge murkily on the printed page. Give the reader a low-fact diet with a high-jargon content. Sprinkle with polysyllabic words and scramble the syntax. For example, if you doubt a predecessor's methods, don't say: "Jones' methods are questionable." Raise the fog index and the wind velocity by saying: "The quantitative parameters assayed by Jones were analyzed and appeared, according to our intrepretations, to demonstrate significant fluctuations which seem to vacillate diurnally."

The *Humble Hedge* is a gambit whereby you qualify your meaning into nothingness while appearing to be objective. Always convey doubts about your statements. Arrange a retreat from clarity with hedge verbs like *indicate, suggest, appear to be, may,* and *might.* Withdraw with these nouns: *speculation, conjecture, theory,* and *hypothesis.* Hedges can be classified as first, second, and third order or as single, double, and triple-barrelled. A fourth order, the quadribarrelled, is clumsy and should be avoided. A fifth-order hedge, such as "Speculation about etiological factors might possibly suggest that previous investigators may have been wrong," is excessive and very poor form. The sentence could be reduced to a third-order hedge with only slight loss of ambiguity.

Word Wedging is forcing impressive words into sentences where they don't belong. The careful wedger selects his tools meticulously. He prefers abstract terms with scientific or literary overtones, e.g., armamentarium, biome, congeners, continuum, dynamic, esoteric, forme fruste, harvest, kinetics methodology, modality, oncogenesis, parameter, and sophisticated. The following example of artful wedging is from an article in a well known medical journal: "Substances which are immunologically foreign are composed of *autochthonous* materials; these are not diagnostic, but with progressive increase, as seen by serial samples, in association with other suspicious *parameters,* the electrophoretic pattern may become significant as a *predictor.*" Observe the clever mingling of windfoggery, hedging, and wedging — all combining to produce a hieroglyphic obfuscuity.

Richard Reece, M.D.
Associate Editor

to help relieve pain in common anorectal disorders

"non-caine" Diothane®

Diothane—with its chemically distinct "non-caine" anesthetic agent diperodon—provides effective temporary topical anesthetic and emollient actions for soothing relief of anorectal pain. Anesthetic activity is effective and relatively prolonged; sensitization is infrequent. Reports to Merrell on 1,500 patients treated pre- and postoperatively with Diothane Ointment, indicate only 22 developed local skin reactions. Reactions to Diothane have been burning or stinging sensations and a few cases of allergic manifestations. An additional advantage: Diothane Ointment and Suppositories are mildly antiseptic. Prescribe or recommend either form...both are now available.

DIOTHANE OINTMENT

COMPOSITION:
diperodon 1.0%; oxyquinoline benzoate 0.1% in a special ointment base.

INDICATIONS:
Provides temporary palliation of pain that may result from hemorrhoidectomy and from common anorectal disorders such as hemorrhoids, anal fissures, pruritus ani.

DIOTHANE
OINTMENT
Soothing, Temporary Relief of Hemorrhoidal Pain, Rectal Itching
CHILD
PULL APART

DIOTHANE SUPPOSITORIES

COMPOSITION:
Each suppository, weighing approximately 2.6 Gm., contains diperodon 1.0%; urea 10.0%; oxyquinoline benzoate 0.1% in a special hydrophilic suppository base. A unique shape keeps the suppository in intimate contact with mucous membranes.

INDICATIONS:
Provide for temporary palliation of pain caused by hemorrhoids and pruritus ani.

Merrell

THE WM. S. MERRELL COMPANY
Division of Richardson-Merrell Inc.
Cincinnati, Ohio 45215/Weston, Ontario

MINNESOTA MEDICINE
HONOR AWARD

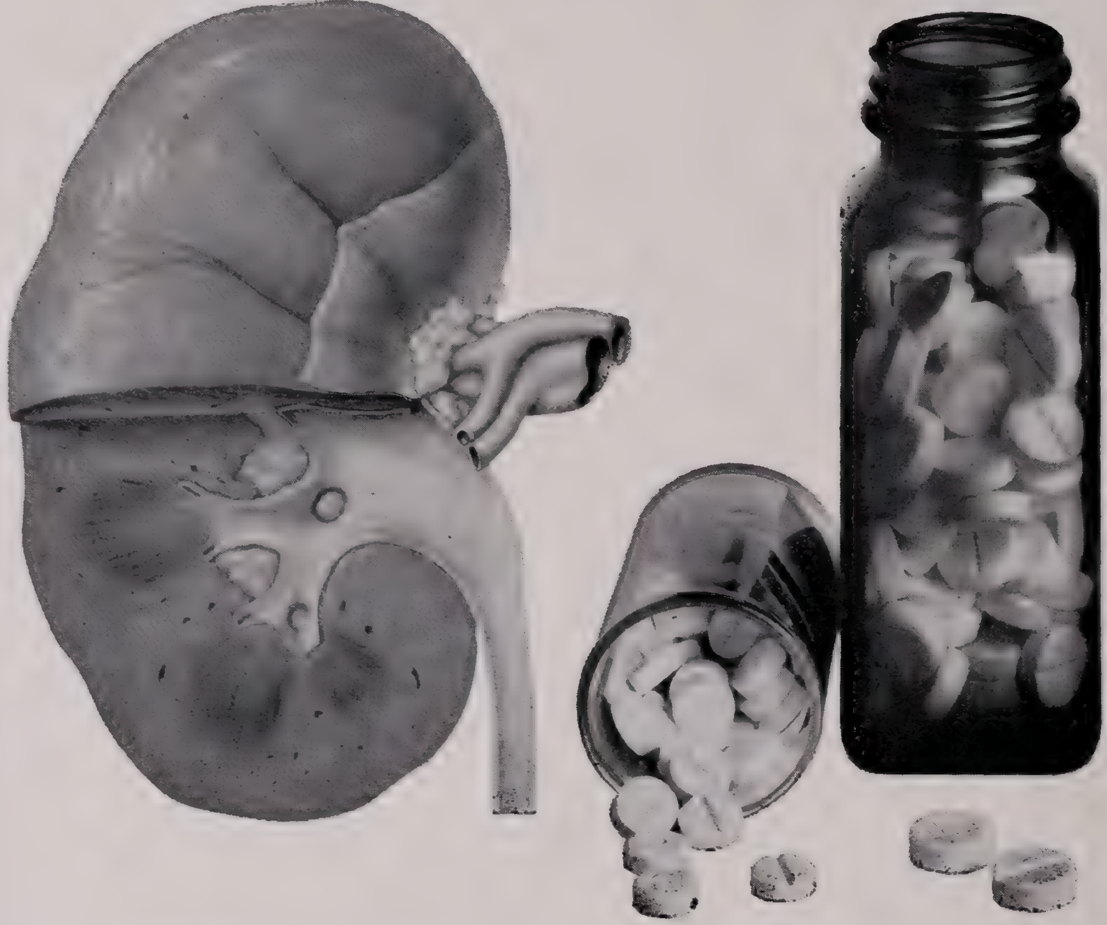
Minnesota Medicine Medical Writing Awards, 1966

It is the pleasure of the Board of Editors to announce the winners of the fifth annual Minnesota Medicine Medical Writing Awards chosen from articles published in MINNESOTA MEDICINE during the year of 1965.

The first place plaque is to be awarded to Dr. Donald M. Yamaguchi of Gardens, California (formerly at the Mayo Clinic in Rochester), Dr. Paul R. Lipscomb and Dr. Edward H. Soule of the Mayo Clinic in Rochester. Their article "Carpal Tunnel Syndrome" appeared in the January issue of MINNESOTA MEDICINE, page 22. The presentation will take place during the annual meeting of the Minnesota State Medical Association in St. Paul at the New Members, County Officers and Delegates Dinner on Sunday, May 15.

Certificates for excellence in medical writing will be awarded to the authors listed on the next page whose article was felt to be particularly outstanding by the Board of Editors.

at Merck Sharp & Dohme...



understanding... precedes development

The development of chlorothiazide and probenecid were events of major importance, but perhaps even more important for the future was the Renal Research Program by which they were developed. When Merck Sharp & Dohme organized this program in 1943, it was expressing in action some of its basic beliefs about research:

- Many problems connected with renal structure and function were still undefined or unsolved. The Renal Research Program would begin its basic research in some of these problem areas.
- From knowledge thus acquired might come clues to the development of new therapeutic agents of significant value to the physician.

For example, the Renal Research Program put fifteen years into this search before chlorothiazide became available. But because these years had first led to a greater understanding of basic problems, the desired criteria for chlorothiazide existed before the drug was developed.

Along with other research teams at Merck Sharp & Dohme, the Renal Research Program continues to add new understanding of basic problems—understanding which will lead to important new therapeutic agents.

MSD MERCK SHARP & DOHME Division of Merck & Co., Inc., West Point, Pa.

where today's theory is tomorrow's therapy

The MINNESOTA MEDICINE

MINNESOTA STATE MEDICAL ASSOCIATION

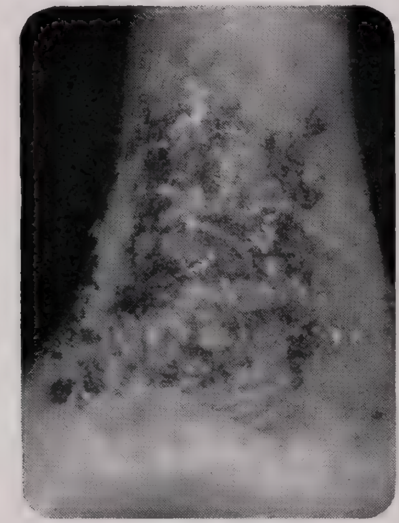
HONOR CERTIFICATE
1966

Manuscript	*Authors*	*1965 Issue*
The Clinician Views Potassium Deficit	W. D. Snively, Jr., M.D. R. L. Westerman, M.D. Evansville, Indiana	June

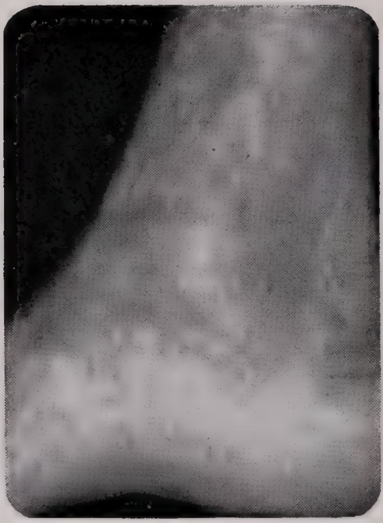
Minnesota Medicine is honored to have this opportunity to acknowledge the work of its distinguished authors and to express to them applause, thanks and cordial best wishes.

Board of Editors

eczema: scourge of childhood



R. R., Age 11—Before treatment—
atopic eczema of long standing



After treatment—with ARISTOCORT
Topical Ointment 0.1% for two weeks

ARISTOCORT® Triamcinolone Acetonide Topicals have proved exceptionally effective in the control of various forms of childhood eczema: allergic, atopic, nummular, psoriatic, and mycotic.

In most cases responsive to topical ARISTOCORT, the 0.1% concentration is sufficiently potent. The 0.5% concentration provides enhanced topical activity for patients requiring additional potency for proper relief.

Administration and Dosage: Apply sparingly to the affected area 3 or 4 times daily. Some cases of psoriasis may be more effectively treated if the 0.1% Cream or Ointment is applied under an occlusive dressing.

Contraindications: Tuberculosis of the skin, herpes simplex, chicken pox and vaccinia.

Precautions and Side Effects: Do not use in the eyes or in the ear (if drum is perforated). A few individuals react unfavorably under certain conditions. If side effects are encountered, the drug should be discontinued and appropriate measures taken. Use on infected areas should be attended with caution and observation, bearing in mind the potential spreading of infection and the advisability of discontinuing therapy and/or initiating antibacterial measures. Generalized dermatological conditions may require systemic corticosteroid therapy. Steroid therapy, although responsible for remissions of dermatoses, especially of allergic origin cannot be expected to prevent recurrence. The use over extensive body areas, with or without occlusive nonpermeable dressings, may result in systemic absorption. Appropriate precautions should be taken. When occlusive nonpermeable dressings are used, miliaria, folliculitis and pyodermas will sometimes develop. Localized atrophy and striae have been reported with the use of steroids by the occlusive technique. When occlusive nonpermeable dressings are used, the physician should be aware of the hazards of suffocation and flammability. The safety of use on pregnant patients has not been firmly established. Thus, do not use in large amounts or for long periods of time on pregnant patients.

Packages: Tubes of 5 Gm. and 15 Gm.; ½ lb. jar.

PHOTOGRAPHS COURTESY OF M. M. NIERMAN, M.D.

Aristocort® Topical Ointment 0.1% and Cream 0.1%, 0.5%
Triamcinolone Acetonide

Also available in foam form and with neomycin.

LEDERLE LABORATORIES, A Division of American Cyanamid Company, Pearl River, New York

618-6

Fifty Years of Honorable Service in Minnesota

The presentation of certificates and pins to Minnesota physicians who have engaged in the practice of medicine for 50 years has become an impressive highlight of each Annual Meeting. According to custom the presentations are made during the course of the Annual Banquet. Few who have witnessed these ceremonies soon forget the setting of such an occasion at which these colleagues with a half century of medical practice to their credit so alertly respond to the roll call.

The custom of honoring Minnesota physicians who have served their patients and communities for a half century was established in 1942. Forty-one physicians were honored at the first ceremony. This group also included those who had passed the 50-year mark prior to 1942.

To be eligible for this award a doctor must have spent the majority of his 50 years practicing medicine in Minnesota.

In 1966 ten doctors were added to the membership rolls of the Fifty Year Club.

Henry E. Binet, M.D.

Dr. Binet practiced medicine almost thirty years in the Range area before his retirement in 1946. He was born at Marquette, Michigan, in July of 1889, and obtained his preliminary education at Marquette, Michigan, and Coleraine, Minnesota. His medical degree was obtained at Northwestern University Medical School in 1916. Immediately following his graduation he returned to Grand Rapids and began his practice in association with Dr. M. N. Hursch. He is a veteran of World War I, where he served in the Army Medical Corps.

First president of the medical society in the Range area, Dr. Binet is a fellow of the American College of surgeons and numerous medical associations. At the present, he is enjoying a well deserved retirement in Grand Rapids.

Bottolf T. Bottolfson, M.D.

Dr. Bottolfson began his practice in Halstad, Minnesota, prior to World War I, but then entered the Medical Corps as a first lieutenant. On his return from the Army he practiced with Dr. A. J. Hageu for three years and thereafter continued in independent private practice at Moorhead, Minnesota, where he has served two terms as mayor and is currently one of the members of their Charter Commission.

Dr. Bottolfson had a wide interest in all fields of medicine and has taken postgraduate courses in Urology, Eye, Ear, Nose and Throat, Neurology and Bronchoscopy in order to keep himself abreast of advancing medical problems.

He is a member of the American College of Surgeons, International College of Surgeons, American Urological Society, North Central Branch of the American Urological Society, Pan American Congress of Ophthalmology and the North Dakota Academy of Ophthalmology and Otolaryngology.

Austin C. Davis, M.D.

Dr. Davis was born at Libertyville, Iowa, on August 12, 1891. His father and one brother were physicians. One of his sons is also a physician.

Dr. Davis finished his elementary education and first two years of college at Parsons College, Fairfield, Iowa, and completed his third year of Liberal Arts and first two years of Medicine at the University of Iowa, from which he received the degree of A.B. in 1913. From 1913-1914 he taught bacteriology at Parsons College and was graduated from Medical School at the University of Iowa in June, 1916. An intern in Internal Medicine during 1916-1917, Dr. Davis was a hospital chemist during the following year.

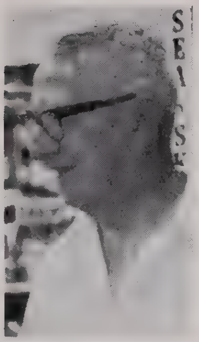
Then he joined the United States Army Medical Corps as a first lieutenant, serving until September 1919. Following military service he returned to the University of Iowa where he served as assistant until July 1, 1923, when he was appointed to the staff of the Mayo Clinic as first assistant, remaining there until his retirement October 1, 1956. His service was in Internal Medicine with particular attention to Endocrinology and was also assistant professor in the Graduate School.

Dr. Davis was a diplomate of the American Board of Internal Medicine, a Fellow of the American Medical Association and a Fellow of the American College of Medicine. He was also a member of Nu Sigma Nu, Sigma Xi, AOA and AFI.

Dr. McClanahan has practiced medicine in White Bear Lake since 1921. He was born in Kirkwood, Illinois, in 1891, and obtained his preliminary education at Monmouth College in Monmouth, Illinois. In 1916 he received his medical degree from Northwestern University Medical School and was licensed that same year in Illinois.

A veteran of World War I, serving in the medical corps, Dr. McClanahan came to Minnesota and was licensed to practice medicine in 1919.

He has served as chief-of-staff at St. John's Hospital in St. Paul and is a member of many national and state medical associations and societies.



Thomas S. McClanahan, M.D.

Dr. McDaniel was born in Bartow, Georgia, on July 14, 1894. He graduated from Emory University, interned at Denver and Rio Grande Hospital in Salida, Colorado. For a period of time he practiced in Virginia, Minnesota, then in Brunswick, Georgia, for about 13 years, and finally returned to Lakeville, Minnesota, where he has practiced up to the present time.

He has one daughter who is director of a three-county Regional Library in Elko, Nevada.

Samuel P. McDaniel, M.D.

Dr. McIntyre was born July 13, 1890, in Davenport, Iowa. After finishing his undergraduate education in Iowa and graduating from Harvard Medical School in 1916, he returned to Iowa to spend his internship. In the First World War he served in the American Expeditionary Force for 15 months and then did postgraduate work at the University of Toulouse, France. He subsequently returned to Minnesota and has practiced in Round Lake and Owatonna to the present date. He was twice Chief of Staff of the Owatonna City Hospital. He continues to do a limited practice up to this moment.

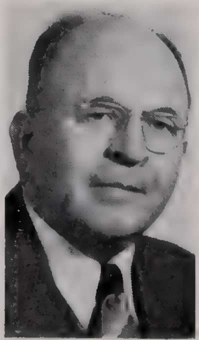
John A. McIntyre, M.D.

Dr. McKinlay was born in Wichita, Kansas, but spent most of his boyhood years in Newkirk, Oklahoma.

After graduation from the University of Kansas School of Medicine, he received his license to practice in the state of Kansas in 1916. Following an internship in Montreal General Hospital, a year of residency in Pathology at the New Haven Hospital, Yale University, service in the U. S. Army and a year of residency at the University of Minnesota Hospital, he started practice in Minneapolis in Internal Medicine in the summer of 1921.

Dr. McKinlay has been a staff member of Asbury, Northwestern, University and General Hospitals and served for a period of time on the Student Health Service, attaining the rank of Associate Clinical Professor of Medicine.

He was a director and later President of the Minnesota Blue Shield for several years and was on the Board of the Minnesota Tuberculosis and Health Association, serving later as President. He has been a member of numerous professional societies including the American College of Physicians. American College of Chest Physicians, Central Society of Clinical Research, Minnesota Pathological Society and the Minneapolis and Minnesota Academies of Medicine.



Chauncey A. McKinlay, M.D.

Continued

John R. McNutt, M.D.

Dr. McNutt was born in New Bethlehem, Pennsylvania, on May 8, 1889. After obtaining his preliminary education at Clarion State Normal High School in New Bethlehem, he received his medical degree from the University of Michigan Medical School in 1916. That same year Dr. McNutt was licensed in Michigan.

In 1918 he went to Two Harbors and practiced there until 1928, specializing in radiology from 1928 through 1930. Shortly afterward he went to Duluth and specialized in radiology, becoming Chief-of-Staff at St. Mary's Hospital in Superior. Later, in 1933, when it was first built, Dr. McNutt opened his office in the Medical Arts Building.

Dr. McNutt was in the first class to be certified in 1935 as a diplomate of the American Board of Radiology and is a fellow of the American College of Radiology. He is also a member of the Radiological Society of North America and American Roentgen Ray Society and a past president of the Minnesota Radiological Society. At one time Dr. McNutt was secretary-treasurer of the Inter-urban County Medical Society.

He is married to Elsie Gerlach, and they have four children.

Joe M. Neal, M.D.

As told by the Department of Insurance News Letter, **Dr. Neal** is an expert story teller, a fine friend and an all-around good fellow. He was a "dean" among insurance personnel, having served in the Veterans Administration in the medical field for more than forty years.

Dr. Neal was born in Gallipolis, Ohio, shortly before the turn of the century. While growing up, he spent his time alternating between his father's drug store and steamboats on the Ohio River. Finally graduating from the College of Pharmacy of Ohio State University, he went into the field of medicine.

He came to Minneapolis in 1916 and served an internship at the Minneapolis General Hospital, and for a period of time he was City Physician and Acting Superintendent.

In 1918 he served in the Army Medical Corps and since then has been interested in the Veterans Administration and their medical problems, serving as a medical consultant in the Disability Insurance Claims Division. Dr. Neal has two children and five grandchildren. He is active in the Masonic Order, the Shrine and the American Legion. Although he is not in practice, he continues to remain active and energetic.

Harry L. Smith, M.D.

Dr. Smith, a specialist in diseases of the heart at the Mayo Clinic from 1928 to 1952, and emeritus professor of medicine in the Mayo Graduate School of Medicine, University of Minnesota at Rochester, was born on September 3, 1887, in Fairport, Missouri. He took the degree of doctor of medicine in 1916 from the State University of Iowa. After an internship in Vancouver, British Columbia, Dr. Smith entered the army in 1917 as a first lieutenant in the Medical Corps. In 1917 he became a diplomate of the National Board of Medical Examiners. After his discharge in 1919, he began the private practice of medicine in Walnut, Iowa, where he remained from 1920 to 1925.

Dr. Smith came to Rochester in June 1925 as a fellow in medicine in the Mayo Graduate School of Medicine. On January 1, 1928, he was appointed to the staff of the Mayo Clinic and in the same year received the degree of master of science in medicine from the University of Minnesota.

Dr. Smith was also professor of medicine in the Mayo Graduate School of Medicine, University of Minnesota at Rochester. He became head of a section of medicine in the Mayo Clinic on July 1, 1945, and a senior consultant in medicine on January 1, 1951. He retired from active practice on October 1, 1952.

In 1936 Dr. Smith was certified as a specialist in cardiovascular diseases by the American Board of Internal Medicine, Inc. He was a fellow of the American College of Physicians, a former president of the Zumbro Valley Medical Society, and a member of the Minnesota State Medical Association, the Minnesota Society of Internal Medicine, the Minnesota Heart Association, the American Heart Association, the Society of the Sigma Xi, the Central Society for Clinical Research, the Alpha Omega Alpha medical honor society and the Nu Sigma Nu professional medical fraternity. During World War II he held the grade of lieutenant colonel in the State Guard in Minnesota.

Curbstone Consultation

QUESTION: My ulcer patient has positive stool guiac tests. His hemoglobin dropped within an 8-hour period from 13 to 12 gram %. Is this significant?

ANSWER: Physiologic variation plus the standard error in hemoglobin determination could account for as much as one gram % difference in hemoglobin level, and therefore, its clinical significance should be interpreted with utmost caution.

QUESTION: What chemical test can I order to help follow the status of my patient with diagnosed hypothyroidism who is being treated with thyroid extract?

ANSWER: The PBI test can be used in this situation to approximate the serum thyroxine level. Most of the PBI measured will be the exogenous thyroid extract. If the patient is being treated with Tri-iodothyronine (Cytomel) the PBI cannot be used, as it will be low.

QUESTION: What is the best screening test for diabetes?

ANSWER: Two-hour post-prandial blood sugar, utilizing a meal containing 100 gm. of carbohydrate.

QUESTION: How soon is the urinary immunologic pregnancy test positive after the last menstrual period?

ANSWER: The excretion of chorionic gonadotropin is at an optimum level from six to 17 weeks after the last menstrual period. A negative result on a specimen obtained prior to six weeks from beginning of last menstrual period should be repeated with a specimen collected after the six weeks.

Edward L. Segal, M.D.*
Martin A. Segal, M.D.*
Ellias N. Manoles, M.D.*
Minneapolis, Minnesota

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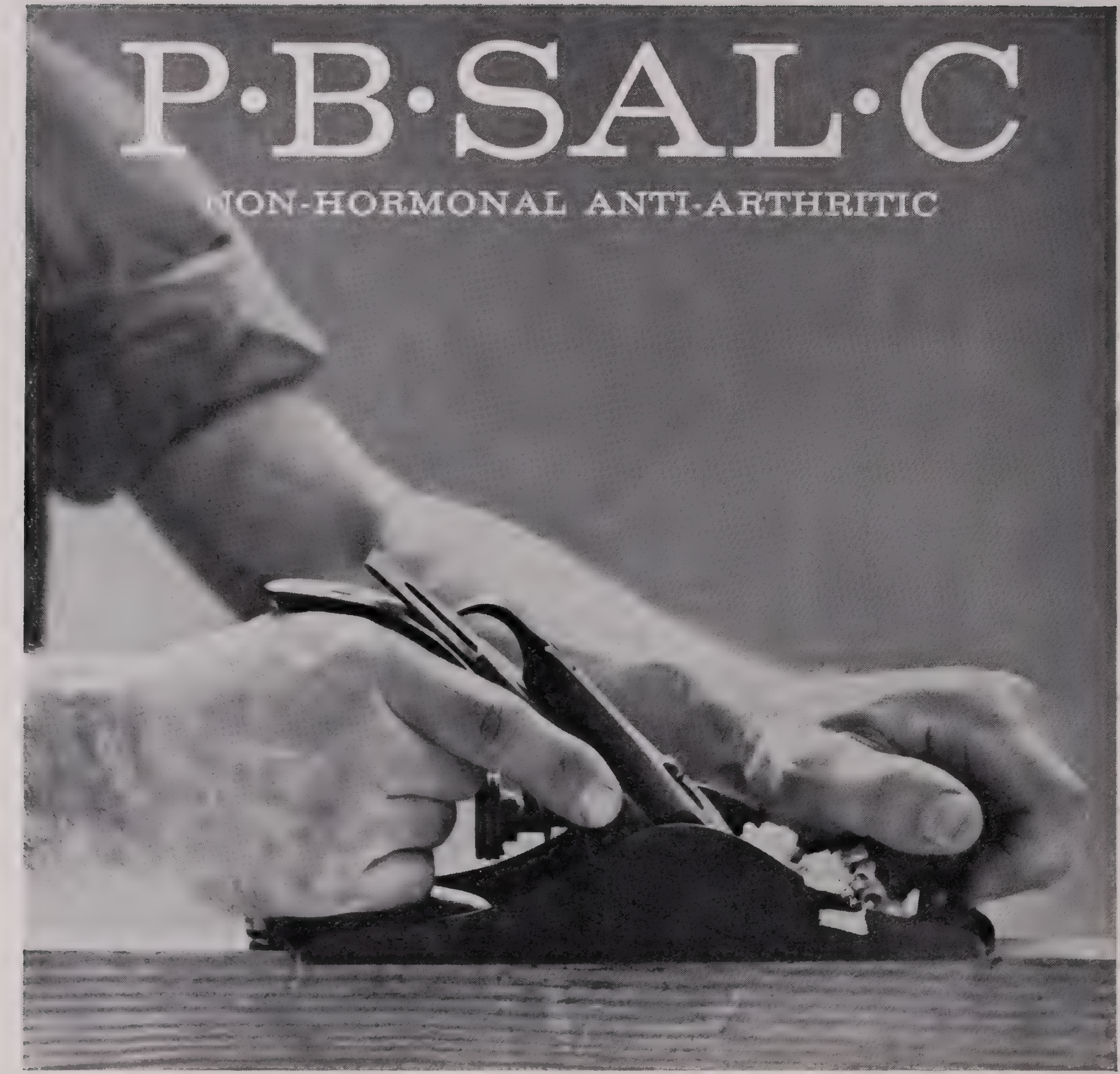
*Methodist Hospital, Department of Pathology.

Trifles make perfection, and perfection is no trifle. — Michelangelo



Helps keep arthritic patients active

P-B-SAL-C is a dependable, effective salicylate formula for relief of pain due to rheumatoid arthritis, bursitis and fibrositis.

Its formula consists of a combination of sodium salicylate, para-aminobenzoic acid and ascorbic acid. This special combination provides higher, longer-lasting analgesic levels compared with salicylates alone. Each P-B-SAL-C Tablet is enteric coated to delay disintegration until it reaches the small intestine.

P-B-SAL-C, low in cost to your arthritic patients, will help keep them active. Other P-B-SAL-C formulas available:

1. P-B-SAL-C with Colchicine
2. P-B-SAL-C with Esoprine
3. P-B-SAL-C Sodium Free
4. P-B-SAL-C with Prednisolene (Sodium Free)

For complete information and samples, write to Dept. 00-105

FORMULA

Each enteric-coated P-B-SAL-C Tablet contains sodium salicylate 0.3 Gm., para-aminobenzoic acid 0.3 Gm., ascorbic acid 50.0 mg.

CONTRAINDICATIONS

Renal damage, salicylate sensitivity or in conjunction with sulfonamide therapy.

DOSAGE

Take 2 tablets four or more times daily.

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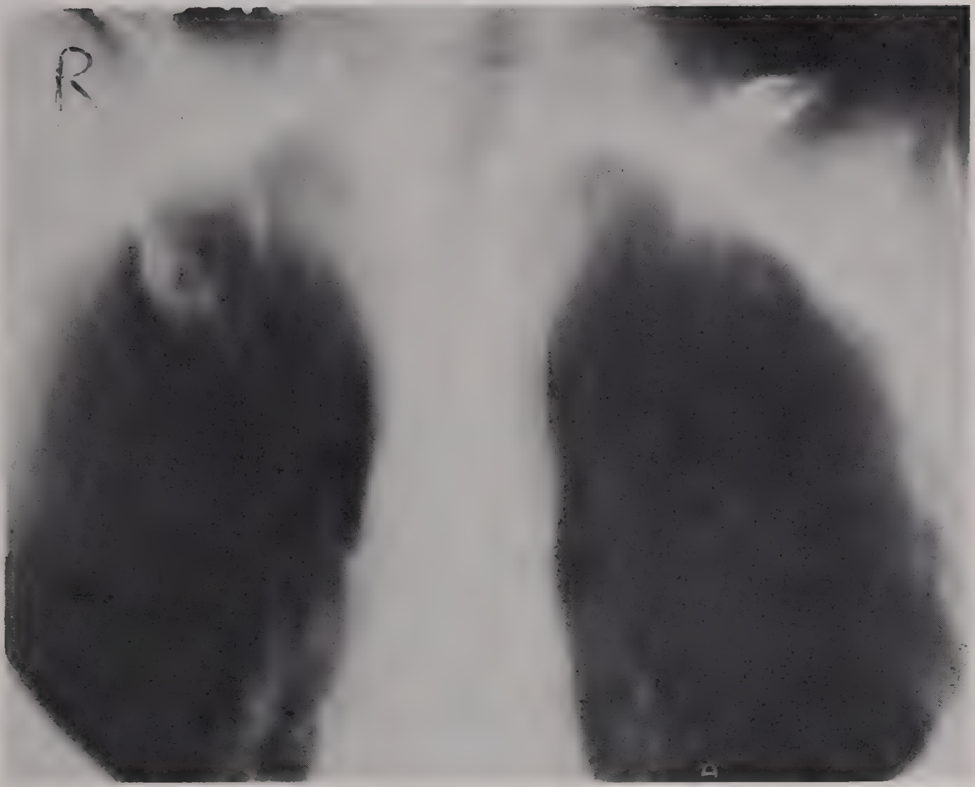
The Viewing Box



This 43-year-old unemployed white male gave a history of chronic cough with production of white sputum, weight loss, and fatigue for the past year. The symptoms became worse during the last three months, together with the appearance of low-grade fever and night sweats. He was a heavy smoker. There was no family history of tuberculosis. Skin tests were negative to old tuberculin 1:1000, histoplasmin, and coccidioidin.

The plain roentgenogram and the planigram (Figure 1) of the chest showed bilateral apical lesions: a nodular density with central cavitation on the right, and a small, thin-walled cavity on the left side.

Among the diagnoses considered were:

1. Tuberculosis.
2. Coccidioidymycosis.
3. Metastatic carcinoma.
4. "Atypical" mycobacterial disease.
5. Cavitating infarcts or embolic abscesses.

What is your diagnosis? (See next page.)

Diagnosis: Pulmonary disease caused by atypical mycobacterium (mycobacteriosis), group III (Battey bacillus).

The "atypical" or "unclassified" mycobacteria may be separated into four groups, according to Runyon:

Group I. Photochromogens (M. kansasii and M. balnei).
Group II. Scotochromogens (M. scrofulaceous).
Group III. Nonphotochromogens, including the Battey bacillus.
Group IV. Rapid growers, including M. fortuitum.

Pulmonary infections caused by the Battey bacillus are most common in the southern and southeastern United States, especially in rural areas of southern Georgia. In these regions the organism has been isolated from the soil and from the throats of healthy persons. The natural habitats of the organisms and the route of infection need further clarification. The disease is generally considered noncommunicable, because conjugal and familial cases are very rare. At the Glen Lake State Sanatorium, we have seen eight cases of clinical disease caused by the Battey bacillus in the past ten years.

The most common symptoms are cough, expectoration, weight loss, weakness and dyspnea. Less frequently noted are hemoptysis, chest pain, and low-grade fever. The diagnosis depends on demonstration of the bacillus by cultures from sputum or resected and biopsy materials. Single isolations with scanty growth of organisms on sputum cultures are likely to be contaminants. However, repeated growth from sputum or resected specimens are significant. Associated or predisposing illness may be emphysema, silicosis, or bronchiectasis. A skin test antigen, PPD-B (purified protein derivative of the Battey strain mycobacterium), is available as an aid in diagnosis.

The roentgen findings of the present case are supposed to be suggestive of mycobacteriosis: (1) large areas of cavitation in relation to the total extent of pulmonary involvement, (2) thin-walled cavity with lack of pericavitary inflammation, and (3) absence of satellite nodules, hilar elevation, bronchogenic spread, and pleural effusion. More often than not, however, these features are absent, and the roentgen picture is indistinguishable from that of pulmonary tuberculosis. Even miliary lesions and large pleural effusions have been encountered.

Treatment is both medical and surgical. Medical treatment is similar to that for tuberculosis, including prolonged multiple drug therapy with streptomycin, isoniazid, para-amino-salicylic acid, and other agents. Resection is strongly indicated if the patient is a suitable candidate for surgery. Early resection and chemotherapy will convert about 75% of the cases to an active status with negative bacteriology, while only 25-30% will satisfactorily respond to medical treatment alone.

W. Y. Yue, M.D.*
Minnetonka, Minnesota
S. H. Tsai, M.D.**
Minneapolis, Minnesota

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*Glen Lake State Sanatorium.
**Department of Radiology, Hennepin County General Hospital.

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3-7 May be secured from the author.

Fracture–Trauma Conference

Arteriovenous Fistula Following a Cervical Stab Wound

IT IS FORTUNATE that deep wounds of the neck are relatively uncommon. A penetrating wound violating the central core of the cervical area is likely to injure one or more of the important vascular, digestive, or respiratory structures therein. Both early and late complications occur with alarming frequency and the over-all mortality may be as high as 11%.[1]

A detailed exploration of cervical wounds requires endotracheal anesthesia and optimum operating room conditions. These may be difficult to obtain at night when many of these injuries occur, and unless a life-threatening condition exists (i. e., hemorrhage or airway obstruction) there seems to be a general tendency for surgeons to treat these wounds conservatively by simply irrigating the points of entry and exit, providing drainage where indicated, and achieving skin closure. This type of treatment will be adequate in certain instances; however, experience has shown that unless an extensive exploration of the wound is accomplished on admission, an unnecessary and disturbing number of delayed or late complications will occur.

An interesting late complication of any penetrating wound is the development of a traumatic arteriovenous fistula. William Hunter first described this formation and Holman established clearly the presenting signs and symptoms.[2] Experience during the Korean War[3] demonstrated the superiority of early reconstruction of at least the arterial channel over the previously recommended quadruple ligation technique. Of patients with carotid to internal jugular vein fistulas, 70% will develop a complication if the condition is allowed to persist for three years.[4]

The following case history illustrates the development of a traumatic arteriovenous fistula and, as suggested by the foregoing discussion, it was felt desirable to correct the defect at the earliest convenient time.

Case History

A 22-year-old male was stabbed in the right chest and right lower cervical area on June 24, 1963. He was admitted to Hennepin County General Hospital in shock; how-

Continued

ever, with blood replacement his vital signs stabilized, and he was taken to the operating room for definitive care of his wounds. Both wounds were copiously irrigated, and when no further bleeding was observed, they were closed. X-rays of the chest revealed no evidence of continued hemorrhage. He was subsequently discharged but was readmitted on July 7, 1963, two weeks after his original injury, because of further bleeding from his chest wound. He was prepared for surgery, a formal exploration of his chest wound was performed by open thoracotomy, and when a severed internal mammary artery was found to be the offending vessel, it was appropriately ligated.

During the second operation the anesthesiologist discovered that a palpable thrill and audible bruit were present over the healed cervical stab wound. On July 17, 1963, a retrograde aortogram was performed, revealing a fistula to be present between the right common carotid artery and the internal jugular vein with a false aneurysm.

The patient was again prepared for surgery. Local anesthesia was utilized early in the procedure, and it was found that a three-and-one-half minute occlusion of the common carotid artery produced no neurological symptoms or signs. General anesthesia was then initiated, and the carotid artery and jugular vein proximal and distal to the fistula were secured with twill tapes. The vessels were then occluded, the fistula taken down, and the false aneurysm resected. In order to prevent constriction of the lumen, a teflon gusset was used to close the rent in the artery. Flow was allowed through the carotid, and the vein was repaired with a running suture of 5-0 silk. The carotid artery had been occluded for thirty-four minutes, and there were no neurological sequelae. The patient's recovery was uneventful.

Discussion

Repair of an open bleeding vessel or of a severely traumatized vessel may be readily accomplished with the generous exposure required for an extensive exploration as advocated. If this had been performed in the case described, the arteriovenous fistula probably would not have developed. It was fortunate that a secondary hemorrhage did not occur, because the massive swelling in the neck accompanying this complication is terrifying to behold and extremely dangerous.

Esophageal wounds as well as blood-vessel wounds may not produce dramatic clinical signs or symptoms in the early post-injury period, but the resultant morbidity and mortality could likely be eliminated if the defect were detected and subsequently repaired during a more thorough initial exploration of the wound.

Expectant treatment of penetrating cervical wounds is not unlike such treatment of similar wounds of the abdomen — fraught with danger. The best course of treatment would appear to be for the surgeon to alert the operating room for a major neck exploration and to prepare himself to properly reconstruct the damaged respiratory, digestive, vascular, and neural structures he may encounter as he systematically performs a search of the wound tract.

Harrison H. Farley, M.D.
Minneapolis, Minnesota

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Derivatively Speaking

Ecchymosis — from Greek *ek* (out) plus *chymos* (juice)

Tumor Conference

An Unusual Breast Cancer

Squamous-Cell Carcinoma Arising in a Tattoo

The usual skin malignancy has little to distinguish it. A recent case had the interesting features of prolonged history, peculiar location, exotic surrounding features, as well as possible involvement of tattoo pigments in the etiology of the squamous-cell carcinoma.

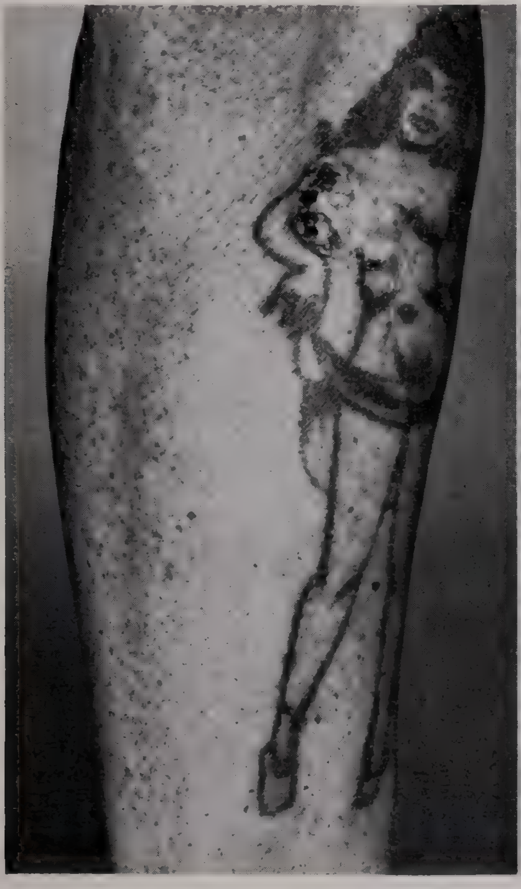

Fig. 1 — A photo of the lesion on the forearm.

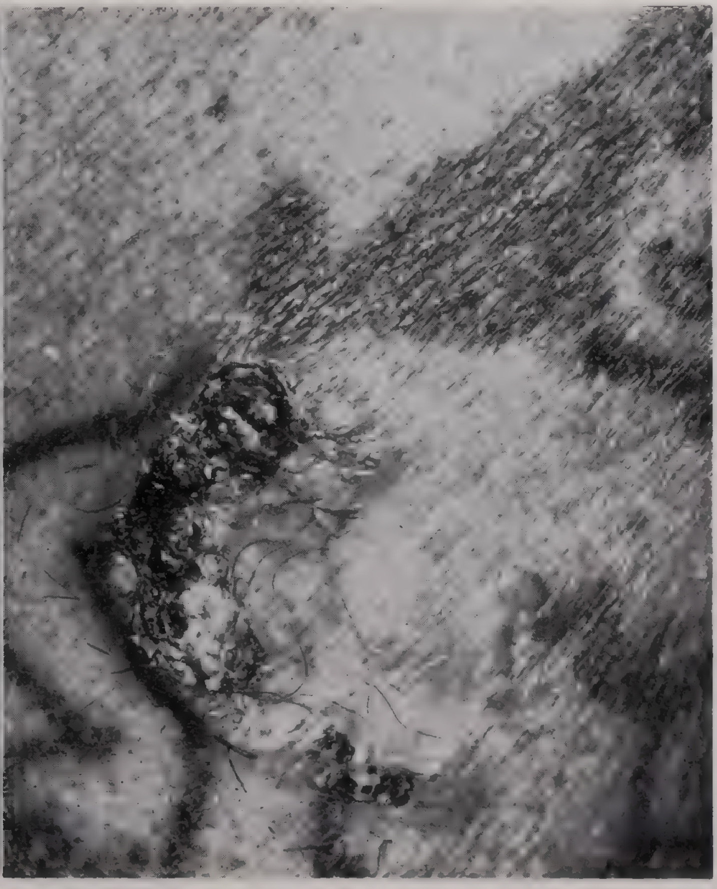

Fig. 2 — A closer view of the lesion showing peripheral spreading from a scarred area.

Continued

Case History

The patient was a 40-year-old active-duty sailor who was seen at our hospital for an infected, raised, scarred lesion in a tattoo on his right forearm. Twenty-one years previously a female figure had been tattooed in blue line on the right forearm. Red pigment had been used for embellishments in the areas of lips, nipples and groin. Ten years ago he noted an itching, scaling, indurated lesion in the area of the red pigment on the figure's nipple. This lesion persisted, essentially unchanged, until four years ago when he scratched the area while working with rose bushes. The area of the tattoo became acutely infected and inflamed. The patient stated that since the acute infection subsided there had been a constantly enlarging, chronically inflamed, itching, raised lesion in the area of the breast of the tattoo. Two years ago he was treated elsewhere with a two-month course of Griseofulvin, without effect. Through the years he had spent much time in the sun.

The patient was a healthy, red-headed, fair-skinned man. The ulcerated lesion was present on the right forearm in the right breast of the tattoo. This is illustrated in Figures 1 and 2.

A biopsy was interpreted as showing squamous-cell carcinoma. Cultures grew only DNA positive staphlococcus. One soft node, (1 x 2 cm.) was felt in the anterior axilla. The patient was admitted to the Plastic Surgery Service and had a wide excision of the lesion. The defect was covered with a split-thickness skin graft. A section from the surgical specimen is shown in Figure 3. Tattoo pigment is easily identified within the tumor (Figure 4). At the time of discharge from the hospital and on two subsequent clinic visits, no axillary nodes could be felt.

Comments

The history of this lesion suggests that there was initially a chronic dermatitis in the area of the red portions of the tattoo with the subsequent development of a squamous-cell carcinoma.

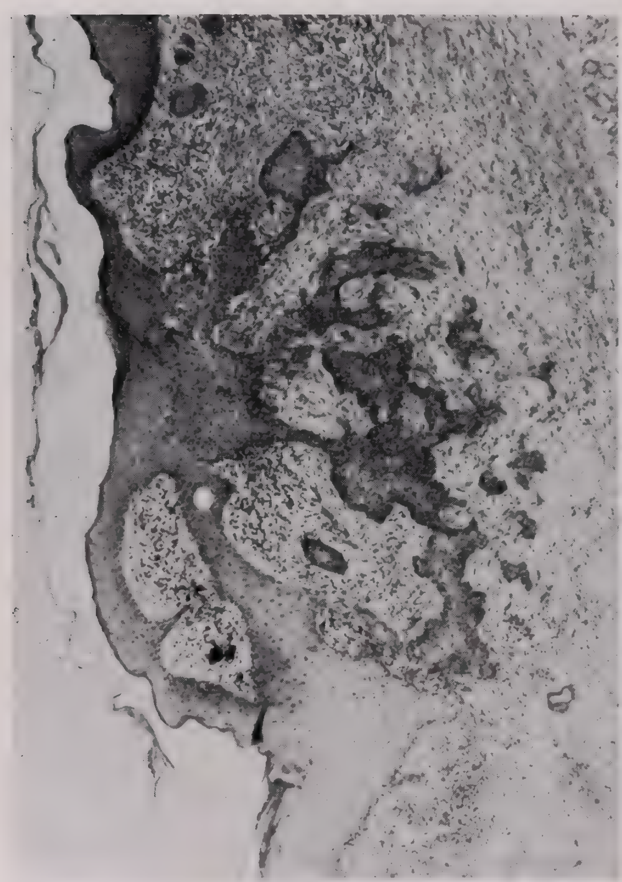

Fig. 3 — A photomicrograph of an area of the tumor containing tattoo pigment.

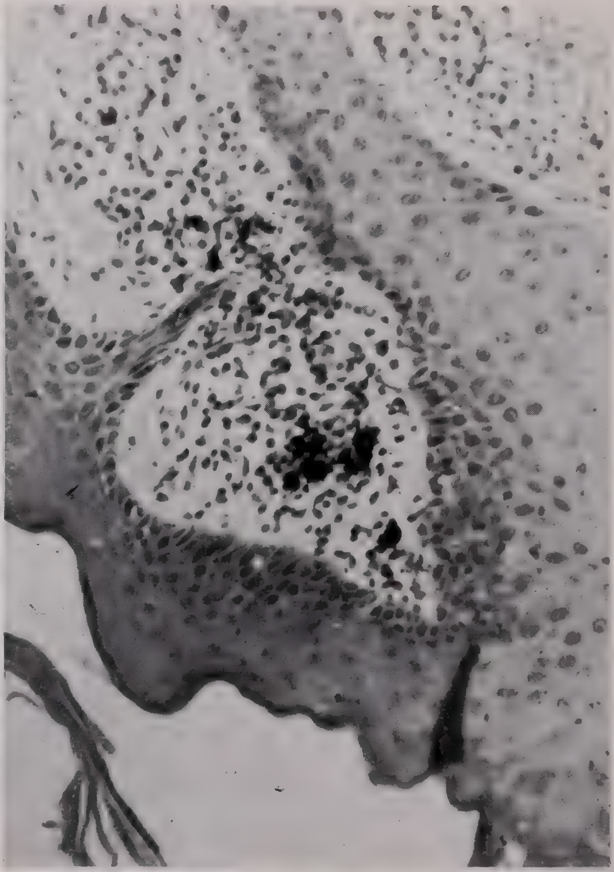

Fig. 4 — A high-powered view of the same area with characteristic tattoo pigments in the tumor area.

The usual red pigment used in tattooing is cinnabar (mercuric sulfide). The other red pigments used are cadmium red (cadmium selenide) and sienna or Mars red (ferric hydrate). Of the many complications of tattooing,[1] one of the more common is a local dermatitis caused by reaction to, or sensitization by, mercury.[2-4] The dermatitis can involve any or all areas of cinnabar tattoo.

It is interesting to speculate as to whether the tattooing agents might have acted as a primary carcinogen or as a co-carcinogen with ultraviolet irradiation. Among the metals, arsenic, nickel, chromium, beryllium, cobalt, selenium, and iron have all been incriminated in some circumstances as carcinogens.[5] Mercury is not included in the usual list of agents. Considering the frequency of tattooing, case reports of malignancy in tattoos are extremely rare.[1]

Sarcoma and melanoma have been found in tattoos, but we are unable to find a previous documented case of squamous-cell carcinoma arising in a tattoo. Squamous-cell carcinoma is an occasional, but well-known, consequence of a long-standing inflammatory process. It would seem more likely that the squamous-cell carcinoma in this case arose secondarily in a chronic dermatitis rather than as a primary response to tattoo pigments.

It is unfortunate that this lesion was observed over the last four years without biopsy, while being treated by several physicians.

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Minneapolis, Minnesota

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*Department of Surgery, Veterans Administration Hospital, Minneapolis, Minnesota and the University of Minnesota, Minneapolis, Minnesota.

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Correction

Medicine in Wright County

In the biographical section of this history — MINNESOTA MEDICINE 45: 673, June, 1962, — a Dr. Edwin Young Clinton is listed. It has since become clear that Dr. Clinton is a ghost and should be disposed of. A thorough research failed to disclose any definite trace of him. There is very little doubt but that there was no Dr. Clinton. His initials, as well as the biographical data, are identical with those of Dr. Edwin Y. Chilton of Howard Lake, Wright County.

Robert Rosenthal, M.D.
St. Paul, Minnesota

Everybody wants to be somebody; nobody wants to grow. — Goethe

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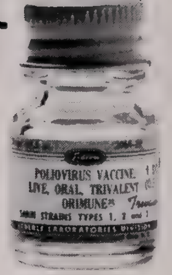

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Neuro-Pediatrics Conference

The Sequelae of Prematurity in a School-Age Child[*]

Dr. Charles Branthaver[**]

The child being evaluated today demonstrates some of the more subtle neurosensory deficits that may result from prematurity. These deficits may not be fully recognized until school-age when certain standards in performance identify the child as deviating from these standards. Prior to this time some suspicion of abnormality may be present which becomes more obvious as the child functions with his peer group.

We have with us representatives from the school which Gail attends in addition to the University staff involved in the evaluation of this child. From this discussion we would hope to achieve a more comprehensive understanding of Gail's performance and ways in which this can be maximally utilized. Dr. Ryan could you give us the initial history and physical findings?

Dr. Dennis Ryan[†]

Gail is a 6-year, 9-month-old white girl who was referred to the University because of a learning problem in kindergarten last year. The school wanted an evaluation of the neurologic aspects of her learning difficulties. Because of the father's antipathy toward doctors there was no referring physician.

Gail was born at the University Hospitals at 31 weeks gestation and weighed 1430 grams (3 lbs., 2 oz.). The labor was uncomplicated and there was no immediate perinatal distress. At 36 hours jaundice was noted and a bilirubin of 13.4 mg. was obtained, rising to 25 mg. at 60 hours of life. Direct and indirect Coombs were negative. The mother's blood type was A positive and Gail's O positive. She was given two exchange transfusions, one at three and the other at five days of age. Her temperature did not stabilize at higher than 97° until the fourth week of life. She did not

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[*] Sponsored by the U. S. Public Health Service Grant N2502A63. These conferences are an integral part of the Comprehensive Clinic Program at the University of Minnesota Hospitals. The pediatrics conferences are held weekly on Wednesdays from 1:00 to 2:00 p.m. The adult conferences are held every Thursday at 4 p.m. Co-ordinators for the project are Dr. Charles Branthaver and Dr. Edward Defoe in Pediatrics, and Dr. Robert Soll, in Adult Neurology.

Held on Wednesday, September 8, 1965, at 1:00 p.m.

[**] Pediatric coordinator. University of Minnesota Hospitals.

[†] Student Physician, University of Minnesota Hospitals.

Continued

regain her birth weight until five weeks of age and did not attain the requisite 5½ lbs. for release from the hospital until two months of age. She was readmitted at three months with an upper respiratory infection and at 10 months with a Salmonella gastroenteritis. At the latter time the pediatric neurologist felt she had a spastic diplegia. The child was then lost to further medical follow-up until her present evaluation. Gail's developmental history is marked by sitting at six to seven months, crawling at nine months, walking by two years, tricycle riding at three to four years and dressing herself at about four to five years. She smiled at one month, spoke a very few words at 18 months and used sentences at about the age of five.

On physical examination Gail is a very thin, active girl who chatters incessantly. She was quite cooperative but tended to perseverate whenever she was "stressed." Her height and weight were below the 30th percentile for six and a half years of age. Head size was normal at 51 cm.

The rest of the physical examination was essentially normal except for the neurologic findings. There was a mild spasticity, greater on the left than on the right, and greater in the lower than the upper extremities. She had hyper-reflexia, a slight circumduction of her foot on running and was able to hop on her right foot, but couldn't hop on her left. Examination in the eye clinic revealed the fundi to be normal. She was myopic, and glasses were prescribed. An audiogram was done and was normal.

She was seen in Physical Medicine and Rehabilitation because of shortening of her left Achilles tendon. Tendon-stretching exercise and special shoes were prescribed. Laboratory studies including Hgb., WBC, ESR, serology, ferric chloride, UA, skull x-rays and sleeping EEG were normal.

Dr. Branthaver

Dr. Schmitt, would you give the neurologic findings?

Dr. Barton Schmitt*

She had no signs of kernicterus** at that time, such as athetosis, paralysis of upper gaze, deafness or cerebellar problems. The only findings were in the lower extremities with spasticity manifested by abnormal hyperactive reflexes, increase in tone with clonus in the left ankle. The spasticity was definitely more prominent on the left but did not interfere with her ambulation except to give her a clumsy gait. We found no abnormalities in the upper extremities.

Dr. Branthaver

This child has a normal EEG in the face of unequivocal signs of an upper motor neurone lesion. Would you discuss the significance of this?

Dr. Schmitt

The EEG records only the electrical activity of the outer 3 mm. of the cortex, and the lesion causing spastic diplegia may well be subcortical, probably an electrically silent one which would not project to the cortex.

Miss Helen Kretchmer†

The mother was a patient here when Gail was born. She was 17 at the time, came from Wyoming and stayed with an aunt. She was in tenth grade when she became pregnant, having left school in ninth grade after failing math. She had Cs and Ds in early high school years and average in tenth grade.

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*Pediatric resident in neurology, University of Minnesota Hospitals.

**See Test Your Word Score Page 779.

†Social worker, University of Minnesota Hospitals.

Gail's stepfather met the mother through her aunt, and this appeared to be an arranged marriage. The couple met in May after Gail's birth and were married in July. He was the youngest of a large family, had asthma, and was "babied." Only two of the family completed high school; Mr. N. completed only ninth grade. He is a very suspicious person and does not associate with persons outside the family. He tolerates Gail when she does not bother him but uses her as an excuse to get angry. He is jealous of his wife and strikes her on occasion, but he has struck Gail only once, as the mother would not tolerate this. The couple has had no children of their own. This is not a happy marriage and Mrs. N. is thinking more strongly of separation and divorce. She has, of late, insisted on Gail's medical care and on being able to associate with neighbors.

The family lives in a two-bedroom trailer park, where there are 200 trailers and 700 people. It is incorporated as a village, and the family has been there for two years.

Mrs. N. said she is convinced that Gail is slow but not retarded. She has observed that the child has periods in which she learns new things, then repeats them for a time. She plays with friends from school and also plays well by herself. She seldom cries but screams after an occasional spanking. When angry, she becomes silent. Our secretary heard her repeat, while waiting alone in the hall, "I'm not retarded, I'm not retarded." Mrs. N. describes Gail as being independent and determined like herself, and there appears to be a very close bond between them. Mrs. N. seems to be growing up and asserting herself more. She went against her husband's wishes to bring Gail here and took a job as a maid in a Howard Johnson motel to earn money for Gail's auxiliary medical expenses. She asked to be told in plain language what Gail's problems are and said she has not had sufficient opportunity to talk with the medical staff here without Gail's presence.

Mrs. Judy Edmonds*

Evaluating Gail's language skills: she is just slightly below her age level in most language skills except those involving the ability to make or understand abstractions through language. She is also slightly below her age level in the ability to recognize forms (seeing a circle for a circle no matter where it is or what it has inside it or around it), and she is quite a bit above her level in the ability to discriminate forms from backgrounds.

Dr. Branthaver

What significance is there in the ability to discriminate forms from backgrounds? Would it indicate more promise to read?

Mrs. Edmonds

I don't attach too much significance to it except that this is an essential skill for learning to read. I think she definitely does very well in that particular area. However, I don't know how well she will understand what

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*Speech therapist, University of Minnesota Hospitals.

she reads because of her difficulty in understanding relationships between things.

Mrs. Grace*

I think that the first thing I noticed that made Gail stand out in the class at school was her incessant chatter, an advanced vocabulary, and an inability to do abstract thinking and to relate one situation to another. Some things she could do extremely well, such as working puzzles and stringing beads. Also, she has an unusually good singing voice; she carries a tune very well and remembers it. She can pick out tunes on the piano just by ear. She worked by herself and rather tended to ignore the other children in the group. As time went on, however, she became a little more interested in the other children, but I don't feel she ever really established what would be a good reciprocal relationship with them. The mother has always been quite objective and understanding with the child and very cooperative in giving us any information that might help us in dealing with her.

Dr. Norman E. Silberberg**

Gail was concrete in her perceptionalization, dealing with things and tangibles rather than abstract concepts; she found it difficult to follow directions for abstract tasks. She was in the low educable mentally retarded range. Recognition vocabulary was significantly higher than her expressive vocabulary; that is, she was able to associate pictures with proper words but was not able to express a definition of the word. She perseverated both verbally and in her motor tasks. She had difficulty in integrating parts of wholes and also showed several tendencies to rotate what she saw; for example, she assembled a puzzle upside down; also, when she was asked to write her name, she was able to get the first two letters correct but rotated the G and the A. In some places where it involved assembly of parts into wholes, she was able to name the parts correctly but unable to place them in meaningful proximity to each other. Her auditory perception seemed quite good and she was able to repeat words perfectly even though she was unable to understand their meaning. Possibly, she may learn to read if her visual perception develops to the point where she can then use a more phonetic approach to this skill.

We decided to retain Gail in kindergarten for one more year to give Mrs. N. some added time to seek medical help, and we hope that time may develop in her an understanding of the social amenities in the class in terms of abstract relationships. Following the second year in kindergarten, she is to be placed in a special classroom for the educable mentally retarded, unless there is some medical treatment which might change the current functioning level.

Dr. Harold Ireton†

Recent intelligence and related testing was supplemented by screening for achievement (reading, arithmetic), visual discrimination (matching geometric forms), and visual-motor coordination (copying geometric designs). At face value, intelligence testing indicates functioning in the borderline retarded range (verbal IQ 79, performance IQ 74, full scale IQ 74). However, certain discrepancies within intelligence testing as well as other test results point to the need for more complex definition. Intelligence test results are characterized by scatter among the subtests, including average arithmetic and vocabulary. Gail's Goodenough Drawing is also average for her age. Her reading achievement is appropriate at grade level 1.1.

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*Kindergarten teacher, Carver Consolidated School District.

**School psychologist, Carver Consolidated School District.

†Child psychologist, University of Minnesota Hospitals.

On the negative side she demonstrates visual motor coordination somewhat under age five. Over-all, the picture is one of a child who is retarded in some areas of intellectual development but not in others; who has probable difficulties in visual motor coordination, but not in visual discrimination per se; who has difficulties in paying attention and in concentrating and is consequently inefficient in her intellectual operations. While the above configuration suggests possible involvement of the central nervous system, the important point is that while she is retarded in some respects, her educational program should probably be geared to dealing with her problems in attention and concentration and her difficulties with complex coordination. This could probably be best accomplished by having her repeat kindergarten. The label 'retarded' might best be reserved; at present it has only descriptive significance and may be misleading.

Dr. Branthaver

Your one outstanding finding has been the child's difficulty in abstraction. She seems to be well below her age in this regard. Wouldn't this be a rather serious deterrent to achievement and isn't this perhaps a more valid sign of retardation?

Mrs. Edmonds

I think Gail's inability to understand abstractions is, to a large extent, due to the fact that she doesn't understand verbal instructions. They are abstract, and she responds with long, impressive, but quite inappropriate sentences. I think that verbal instructions will have to be supported by example, by dealing with concrete materials, or any other means you can use to help her understand what it is you want her to do.

Dr. Branthaver

Spastic diplegia and impaired intelligence are not unusual sequelae of prematurity. Of all patients with cerebral palsy, 30% are prematures; and of those prematures who have cerebral palsy, 70% have spastic diplegia.[1,2] In one study on spastic paraplegia only 7½% were retarded, which indicates that the two deficits are not necessarily related. Cecil M. Drillien[3] studied 50 prematures in Scotland after they had reached school age. One half were not educable in the regular school; 25% were in the dull range of intellectual functioning and having difficulty in the regular school. The remaining 25% were in the regular school and doing well. A large number (88%) were having behavior problems, though not characteristic of the pattern seen in the minimal cerebral dysfunction syndrome. In another study by Heimer et al.[4] it was found that the incidence of neurologic sequelae correlated significantly with low birth weight and low, unstable body temperature. Lubchenco et al.,[5] in 1963, reported on a group of prematures (birth weight 3 lbs., 4 oz. or less) who were about 10 years of age. Fifty per cent of these children had neurosensory deficits, with 60% having abnormal electroencephalograms. Their school problems were not

Continued

correlated with their IQs since 20 of 35 with normal IQs were having serious academic problems. It is of interest to note that these sequelae did not correlate with the serum bilirubin but did with the low birth weight. This is quite a different prognostic picture than was thought to be true a few years ago.

Dr. Ryan

All this child needs in the way of physical therapy is some stretching exercise to correct the shortened Achilles tendon; the mother has been instructed in this. In addition, corrective shoes have been prescribed.

Dr. Branthaver

The spasticity is not a serious problem, nor does it require extensive therapy. The only problem that might arise would be whether the tendons were so tight as to make her gait difficult. However, the spasticity should not interfere with the over-all planning for Gail's educational program. Whether she should be in the regular or special education classes can be decided only by the school authorities after appropriate observation and evaluation. The mother would like some final decision as to whether Gail is or is not a retarded child. We will attempt to answer this in as direct and honest a way as possible, namely, that she is educable but will have learning problems which will need special management.

Dr. Edward Defoe[†]

I think it should be made clear, however, that the University is not able to offer total on-going medical care.

Miss Kretchmer

In view of the father's antagonism toward physicians, I would expect that Gail would not be under a physician's care in her community. What continuing supervision might be available?

Dr. Branthaver

I don't visualize any significant change taking place in the father's attitudes, since he has not involved himself in Gail's problem. We are left with the school taking responsibility for the educational program and the University continuing to be responsible for her minor motor dysfunction. On the positive side, we have a responsible mother who probably will seek help as significant problems arise and will be receptive to suggestions given by the school.

In summary, we have a child who has neurosensory deficits as sequelae of a premature birth. Her learning handicaps are such that special instruction may well be essential, and some methods of approach have been discussed. The decision relative to the management of her educational program must rest completely with the school. Her spastic diplegia is mild and should not prove to be a significant handicap. There is need of continuing medical supervision, and this can be provided through the Physical Medicine and Rehabilitation Department here at the University Hospital. If necessary medical supervision can be offered, though less adequately, through the general pediatric outpatient clinic.

I would like to express my appreciation for the participation by Mr.

[†] Pediatrician, University of Minnesota Hospitals.

Karnuth, Mrs. Grace and Dr. Silberberg from the school district. Without their contributions this evaluation would not have been possible.

Charles Branthaver, M.D.
University of Minnesota Hospitals

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Mildew on the Little Black Bag

Tradition has associated the physician with the little black bag: the universal and esteemed signal that here comes, or there goes, the doctor. The bag may be new; it may be old or even dilapidated; whatever its condition it is the visiting physician's exclusive hallmark. His distinctive charisma derives, not from his clothes, his manner, his conveyance, but from the little black bag he carries.

The doctor and the little black bag are a team. A house call without the bag is a disappointment, if not an affront, to the patient, the family, and even the neighbors. It is almost a breach of promise!

The official opening of the bag at the bedside is invested with a ceremonial aura of expectancy that gives courage to the patient and hope to the family. No one, neither the patient nor the bystanders, not even the doctor himself, knows exactly what the bag contains. From its mysterious depths can be extracted one by one an incredible assortment of instruments for examinations, needles for injections, drugs for sedation or therapy, not to mention other incidentals with wholly arcane functions.

Every physician has a personal and symbiotic attachment to his bag. Dr. Bagley (no pun intended) recently said: "You cannot carry a little black bag for years without making a lasting friendship with it. Further, the bag readily makes friends with the patients." Telephone advice, office, clinic, or hospital care can never assure the physician of the family's confidence that follows a house call with the little black bag. There is no substitute for it; from it emerges for the physician an invaluable graduate training, inaccessible to the doctor without the experience of house calls in company with the little black bag.

Hippocrates may or may not have had a little black bag to carry about with him; but the oath states: "Into whatever *houses* I enter, I will go to the aid of the sick." There is no place like the patient's home and bedside to learn the art of medicine — with the little black bag at his and your service.

Therefore, preserve that charismatic little bag, carry it, and use it. And some quiet evening place it reverently beside you as you doze in the rocking-chair and reflect on the sorrow and joy, the failure and success, the sacrifice and devotion you and the little black bag have so profitably and intimately shared together.

George M. Fister, M.D.
Ogden, Utah

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Medical Seminar

Biologic Defiance to Transplantation

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THE PROSPECT OF treating patients by replacing diseased organs with allogeneic transplants of normal organs (homografts in the old terminology) has become a major concern of experimental medicine in recent years. The vast literature on the subject includes reports showing that virtually every organ and tissue have been used as allograft material in a wide variety of experimental settings. Except for a few special situations, such attempts have fallen short of complete success because within a few days or weeks the grafted material is destroyed by the recipient. This phenomenon is termed "rejection" and constitutes the prime obstacle to successful allogeneic transplantation. A consideration of the rejection reaction is the subject of this presentation.

A simple observation demonstrates that the rejection reaction to allografted tissue is an immune reaction. In the first encounter of an unmodified recipient mouse with an allograft of skin, destruction of the graft occurs and rejection is complete in about 10 days. This is termed the "first-set reaction." However, when the recipient is challenged a second time by an allograft from the same donor, rejection is greatly accelerated and may be complete in five days or less. This is termed the "second-set reaction" and constitutes a typical immunologic, anamnestic* response. Contact of the antigen, namely the allograft, with the immunologically competent recipient must take place before the reaction can occur and graft necrosis is the result.

The rejection reaction arises in an artificial setting and has no natural counterpart. Therefore, it seems more appropriate to use the term "biologic" rather than "physiologic" with respect to the host's defiance to transplantation. The "physiologic" significance of this mechanism, if there is one, is unknown.

Genetic Considerations

The description of the rejection reaction includes some pertinent genetic considerations. The rejection reaction will not take place when a transplant is made between identical twins. Similarly, a genetically uniform population of experimental animals, for example, an isologous strain of mice produced by inbreeding (repeated brother and sister matings over many generations) will freely accept grafts from one another without incident. However, a graft from a male to a female of the same inbred strain, by definition, introduces a genetic dissimilarity since the female does not possess the "y" chromosome of the male. This graft may therefore be rejected in some strains.

Hybrid Offspring

When a member of one strain is crossed with a member of a different strain, the resultant F_1 hybrid offspring will possess the genetic characteristics of both strains. The offspring will accept a graft from either parent without a rejection reaction occurring. By contrast, a member of either inbred parental strain will not accept a graft from the F_1 generation hybrid because the hybrid possesses antigens not shared by either parent alone. Subsequent crossbreeding with

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*See Test Your Word Score Page 779.

still other strains introduces additional genetic dissimilarity and results in a stronger rejection reaction when a graft is attempted to a member of any of the parental strains.

Mongrel Offspring

A mongrel population, such as the human population, introduces the possibility of a relatively large number of genetic dissimilarities between individuals. It may be anticipated that a graft from an individual in this population will be rejected by most others of that population. Therefore, genetic factors are of fundamental importance in determining the occurrence of the rejection reaction in the host.

Why does genetic dissimilarity permit allograft rejection? In order for an antigen to perform as such, the host's reticuloendothelial system must recognize that antigen as foreign to itself. In the antigenic donor cells, it is not the genetic material per se (the DNA) which is recognized as antigenic by the host. Rather, the genetic material merely performs its usual duty of directing the production of the various molecules concerned with normal cell structure and economy. These resultant molecules will differ slightly from one individual to another, reflecting genetic dissimilarities. Furthermore, it is these molecules, the normal components of the graft cells, which are antigenic and treated as such by the graft recipient. These molecules, when considered in the context of transplantation, are termed "transplantation antigens." Similarly, the specific genes responsible for their production are termed "histocompatibility genes." Since the classical concept of the "gene" is no longer adequately defined, perhaps it would be preferable to term the latter "histocompatibility loci" on DNA molecules.

Inbreeding

Sophisticated experiments involving inbred mice of known genetic composition have given evidence of a number of histocompatibility loci. By selective breeding techniques, these loci can be tested individually or in combination in terms of their ability to induce a rejection reaction. A graft that differs from its host in only a few loci will be rejected much more slowly and with a less violent reaction than one with a high degree of genetic dissimilarity. Such experiments also have demonstrated that individual histocompatibility loci differ in the strength with which they will induce a rejection reaction in a recipient that lacks this locus.

The single histocompatibility locus in the mouse that is capable of inducing the strongest rejection reaction is termed the H-2 locus. (The H-2 locus is one of several so-called "H" loci. Their corresponding antigens are termed "H" antigens. These are termed "H" loci and "H" antigens because early work demonstrated their conspicuous ability to induce formation of "hemagglutinating" antibody. Their function as transplantation antigens, however, has subsequently been clearly established.) This H-2 locus is probably composed of 20 alleles and is responsible for the existence of several transplantation antigens in the cell.

Immunofluorescent and fractionation techniques have demonstrated that these H-2 derived antigens probably are located in the cell membrane and intracellular membranous structures and, chemically, are believed to be lipoproteins. It is interesting that the H-2 derived antigens seem to undergo maturation. They are relatively weak immediately after birth, but rapidly increase in potency and achieve about 50% of their adult potency by nine days of age.

Such detailed genetic information results from studies carried out in mice, but similar data are not available for other species, including man.

Immunologic Considerations

What happens when an allograft is applied? Basically, three things take place. There is (1) a local host cellular response, (2) rejection and destruction of the graft, and (3) the appearance of circulating antibody. It was pointed out that direct contact of antigen with the reticuloendothelial system of the host is obligatory in order for a rejection reaction to develop. The antigen gains access to the host at the graft-host interface. In organs such as the kidney, this interface is established immediately by uniting the graft and host blood vessels in the technique of grafting. The interface, then, consists of the vascular endothelium of the graft and the bloodstream of the host.

The graft-host interface is somewhat different in skin grafts. Vascular channels develop only as healing proceeds. But these channels are not essential for sensitization to occur, since repeated removal and replacement of the graft, preventing establishment of vascular channels, does not prevent sensitization. Therefore, the graft bed itself is the interface, and cell debris is the antigen. The graft bed later becomes the site of intense infiltration by host cells, confirming the local reaction to the graft.

Having entered the host circulation, antigen exerts a systemic effect on the host lymphoid tissue. In skin grafts, the regional lymph nodes draining the graft site are the first to show this effect, but soon distant lymphoid tissue is affected.

Morphologic evidence of this encounter between lymphoid tissue and antigen becomes evident at about three days after grafting. Large pyroninophilic cells appear and proliferate, causing enlargement of germinal centers. Under the electron microscope, small clusters of ribosomes and little endoplasmic reticula are evident in the cytoplasm of these cells. As time passes, plasma cells, with extensive endoplasmic reticula and many ribosomes, appear in increasing numbers. Maximal activation occurs on about the ninth day.

The development of this reaction in host lymphoid tissue is associated with the appearance of a cellular reaction at the graft site and the appearance of gamma globulin antibodies of several types, including hemolysins, hemagglutinins, and cytotoxins. Considerable controversy has raged regarding the relative importance of the cellular response versus the humoral response in the development of the rejection reaction.

Some investigators have stated the belief that cells are essential to the rejection reaction. These "cellular theorists," championed by Medawar, stress the importance of cell-bound antibody and the local cellular reaction. One of their main arguments concerns the observation that transplantation immunity cannot be passively transferred to an indifferent animal by antibody-containing serum but can be transferred by sensitized lymphocytes.

Other investigators assert the role of circulating antibody in the rejection reaction. These "humoral theorists," led by Stetson, have demonstrated that immunity to a transplant can indeed be passively transferred by serum if the graft consists of single cells rather than an aggregate of a large number of cells in a tissue or organ.

Both the "cellular" and "humoral" theories of allograft rejection are supported by much additional data. The importance of cells is suggested by the fact that the layer of sensitized host mononuclear cells surrounds a skin graft undergoing rejection. If, however, the graft is enclosed in a millipore chamber such that the host cells are prevented from directly contacting the graft, the graft is preserved.

The importance of humoral factors is by no means excluded by these data. There is valid evidence that the millipore chamber not only excludes host cells but also prevents circulating antibody and complement from reaching the graft in significant concentrations. Furthermore, accelerated graft rejection may indeed be accomplished with passive transfer of circulating antibody to an indifferent animal. This can only be achieved, however, if the antibody is harvested at the height of the initial rejection reaction. This capacity is not present in immune serum harvested at a later time, or after repeated stimulation with graft antigen, even though antibody titers become much higher. This indicates that "early-appearing" antibody differs from "late-appearing" antibody. Earlier work demonstrating the ineffectiveness of passively transferred humoral antibody employed only the ineffective "late-appearing" antibody.

It is interesting that "early" and "late" antibodies can be distinguished chemically. Initial antigenic stimulation elicits an anti-

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body response of the 19S (immunoglobulin M) variety. In contrast, the antibodies elicited in the anamnestic response are of the 7S (immunoglobulin G) type. Although this difference has been observed, the relation between antibody type and the ability to induce passive graft sensitization is unknown.

Regarding the nature of cell-bound immunity, it has been pointed out that transfer of sensitized lymphocytes to an indifferent animal will impart sensitization to that animal. If these cells are tagged with a radioisotope, they distribute themselves throughout the lymphoid system of the host. When the animal is subsequently challenged by an allograft, the host's cells (but not the injected tagged cells) appear at the graft site where rejection takes place. A similar passive sensitization can be achieved even if the transferred sensitized lymphocytes are enclosed in a millipore chamber, preventing direct contact with the unsensitized host. Sensitized cells thus are capable of imparting sensitization to other immunologically competent cells, and the existence of a subcellular factor capable of leaving the millipore chamber to effect this is suggested.

Subsequent work has led to the demonstration of just such a "transfer factor" with this property in extracts of human and rodent lymphocytes. This factor is effective in imparting enduring sensitization in minute quantities. Injection of as little as 0.1 ml. of a cell-free lymphocyte extract will be effective. The exact identity of this factor is unknown, but it seems to withstand freezing, distilled water lysis, and treatment with desoxyribonuclease, ribonuclease, or trypsin. Despite the apparent ribonuclease resistance, other investigators have achieved the "transfer effect" by direct use of RNA extracted from sensitized cells. Further work is needed to reconcile these views.

Thus it has been shown that the act of transplantation results in observable changes in the immunologically competent lymphoid tissue of the host. Theories regarding the mechanism by which activated lymphoid tissue effects graft rejection have stressed the importance of cellular and humoral factors. To date, the relative significance of these mechanisms in allograft rejection is unknown.

The Host-Versus-Graft Reaction

Certain events take place within the graft itself. Although full antibody response does not develop for several days after transplantation, there is an immediate interaction of graft and host that touches off the chain of events leading to rejection. Although the precise role of cell-bound and circulating antibody is ill defined, such antibody can be regarded logically as being essential to the rejection reaction. It is generally conceded that graft-cell destruction may be accomplished by combinations of antibody with antigen in the presence of complement. The obvious site for damage to appear first is the graft-host interface. Since the blood supply to the kidney is established in the technique of transplantation, the kidney allograft differs considerably from, for example, a skin graft, and a detailed look at the sequence of events taking place in the allografted kidney is worth considering.

In experimental animals, small lymphocytes make contact with capillary endothelium almost immediately after the kidney is transplanted. Two or three days later, cells that appear to be large lymphocytes or histiocytes are seen clinging to the peritubular capillary endothelium. The intervening cell membranes between endothelial and mononuclear cells quickly disappear, and cytoplasmic continuity is established. Resultant endothelial damage encourages deposition of fibrin, platelets, and cell debris. Progressive narrowing of the graft vessels ensues, blood perfusion diminishes, and ultimately signs of infarction and necrosis become apparent. Interruption of the blood supply has efficiently ended the life of the organ.

The predominating vascular reaction is accompanied by a progressive increase in plasma cells and deposition of gamma globulin on the media of the interlobular arteries. Terminally, there is increasing edema and infiltration with neutrophils and macrophages. All function ceases between the fifth to the eighth day.

That the blood supply to the kidney is established in the technique of grafting distinguishes the kidney transplant from the skin transplant. It has been shown earlier that vascularization of the skin graft is not necessary for sensitization to occur. Similarly, vascularization is not necessary for skin graft rejection. This is exemplified by the so-called "white graft" reaction. This occurs when a second skin graft is applied to an individual previously highly sensitized and is demonstrated especially easily in rabbits. The reaction is so violent and rejection so rapid that there is no chance for vascularization of the ischemic graft to take place.

Summary and Conclusion

The rejection reaction is basically an immune one. It is permitted to develop, fundamentally because genetic dissimilarities exist between graft and host. Genetic dissimilarities are reflected in dissimilar molecular cell constituents which the host recognizes as antigenic. Histologic evidence that the host has encountered graft antigen appears within host lymphoid tissue. Shortly thereafter, humoral antibody appears and a local cellular reaction develops at the graft site. The graft is subsequently destroyed. Current data do not permit a definitive statement as to the relative importance of circulating and cell-bound antibody in the rejection reaction.

Transplantation, as such, is a man-made artefact. With the possible exception of pregnancy, it has no known natural counterpart. The physiologic justification for the existence of the observed reaction to a graft is not understood. Could it be that this is a normal homeostatic mechanism suppressing the proliferation of cells undergoing neoplastic transformation? Why, then, are the genetic alterations in neoplastic cells not recognized as such and destroyed in all cases? Although specific antigen and anti-tumor antibody have indeed been demonstrated, could there be a breakdown at some point in a "natural" rejection reaction?

In the final analysis, the greatest ultimate benefit from transplantation research may not be the successful transplantation of organs at all, but rather a deeper understanding of the function of the immune system and its clinical significance.

Leo R. Zacharski, M.D.*
Rochester, Minnesota

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*Mayo Graduate School of Medicine (University of Minnesota), Rochester: Resident in Medicine.

Pharmacopoeia of the Colonial Physician

His pharmacopoeia consisted mainly of simples, . . . St. John's wort and Clown's All-heal, with Spurge and Fennel, Saffron and Parsley, Elder and Snakeroot, with opium in some form, and roasted rhubarb and the Four Great Cold Seeds, and the two Resins . . . with the more familiar Scammony and Jalap and Black Hellebore. . . . He would order Iron now and then and possibly an occasional dose of Antimony. He would perhaps have had a rheumatic patient wrapped in the skin of a wolf or wild cat, and in case of a malignant fever with 'purples' . . . or for an obstinate king's evil he might have prescribed a certain black powder, which had been made by calcining toads in an earthen pot. . . . Sydenham had not yet cleansed the Pharmacopoeia of its perilous stuff, but there is no doubt that the more sensible doctors of that day knew well enough that a good honest herb-tea which amused the patient and his nurse was all that was required to carry him through all common disorders. — Oliver Wendell Holmes

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Clinical Path Conference

Diarrhea and Anuria

Dr. Robert Good*

This 20-month-old white female was admitted to University of Minnesota Hospitals on April 15, 1963, because of persistent vomiting, a gastrointestional disturbance, and strange behavior which might be attributable to disease of the central nervous system. She experienced an upper respiratory infection which began April 5, 1963, and was treated with aspirin.

Anorexia occurred on April 11, 1963, followed by one large emesis the next evening. On April 13 vomiting followed each meal, and the vomitus was said to contain black flecks. Following this the child began to pass green and brown-black liquid stools. Her parents noted that she slept most of the day and, when awake, would stare in a strange fashion.

On the following day, April 14, she vomited constantly, had four to five liquid green-brown stools, and received one teaspoon of a paregoric-kaopectate preparation every two to three hours. She retained some of this medication plus some carbonated beverage. Because of the diarrhea, it was not known whether she had urinated during the day prior to admission.

According to the history she had been slow in her development. She didn't sit until she was ten months of age; she didn't walk until she was twenty months. She required a gastric lavage three weeks prior to admission because of Enovid ingestion. The family used well water and was having difficulty with a partially obstructed cesspool.

Physical Findings

She was a pale, acutely ill, motionless, staring child reclining with flexed knees and exhibiting an occasional loose cough. Vital signs were BP 90/60, R 22, P 140, and T 98. The temperature is significant. Findings included a flat, scaphoid abdomen and guarding in both lower quadrants. She had some abdominal tenderness, moderately hypoactive bowel sounds, and questionable bilateral costovertebral angle tenderness.

Laboratory Findings

The admission hemoglobin was 11.6 and the white blood count 64,250. She had 80% polymorphonuclear leukocytes, 18% lymphocytes, and 2% mononuclear cells. Prior to the intravenous therapy the serum electrolytes were within the normal range. No acidosis was present. Her sodium concentration was normal, but her BUN was elevated to 57 mg.%. Initial fluids consisted of 100 cc. of plasma every two hours followed by a ⅓ N saline flush of 150 cc. in 45 minutes. Because of failure to void, ⅓ N saline was continued at 1200 cc/M^2/day.

At 8 a.m. on the morning of admission a peritoneal tap and a spinal tap were performed. The peritoneal fluid showed red blood cells and white blood cells and a significant amount of protein, 1.6 gram%. The lumbar tap showed a normal opening pressure of 130 mm. The protein and sugar were normal. There were red blood cells, however, in the tap. No indication is given as to whether or not trauma was associated with the tap.

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*Professor, Department of Pediatrics, University of Minnesota.

Progress

At 10 a.m. the blood pressure was recorded and found to be elevated at 140/90. Intermittent tonic movements of the limbs were noted, and the child had seizures followed by two grand-mal seizures without evidence of focal origin. Blood was drawn and showed a sodium of 127 mEq/L. and a potassium of 4.2 mEq/L. The chloride was 87 mEq/L. and the CO_2 18 mEq/L. The BUN had gone up to 62 mg.%, sugar was 187 mg.%, calcium 8.2 mg.%, and the magnesium 2.1 mEq/L. — a normal value. But the physicians were unaware of the electrolyte data, and a 125 cc. of ⅓ N saline was given for over a one-hour period without resultant voiding. Because of apparent renal shutdown, the fluid therapy was altered to 10% glucose, and distilled water was started at a rate of 500 cc/M^2/day. Fluid intake that day, including plasma, totaled 900 cc.

Another grand-mal seizure occurred. It began with a right-sided tonic movement, became generalized, and was associated with cyanosis and respiratory arrest. The child was successfully resuscitated and given 10 cc. of 3% sodium chloride and 0.75 cc. of intravenous paraldehyde. A repeat white count was 104,000. Any count over 100,000 is supposed to signify leukemia, but I would except this case. I will return to the extremely high white count later.

I consider the ingestion of Enovid establishes the existence of pica.* I am not able, in working out this puzzle, to implicate Enovid as being of any pathogenic significance. Her ingestion of Enovid indicates that this little 20-month-old child was capable of ingesting strange items. A 3-year-old male sibling had a concurrent upper respiratory tract infection without gastrointestinal symptoms. However, the cesspool problem probably is a red herring rather than the red flag, but the well and the plumbing might provide exposure to gram-negative bacterial infection from feces. I think that both the abdominal and costovertebral angle tenderness represent pertinent data. The passage of 3+ guaiac positive stools and of red liquid feces is also important and perhaps critical information.

The serum osmolarity on April 15 was 300 mOsm/L. This is at the upper limits of normal and reflects, I think, either an elevation of the blood urea nitrogen or the retention of other products from renal shutdown.

The blood pressure throughout the first hospital day was elevated. A fairly stable evening was interrupted by occasional spasms and "frog-leg" movements of the extremities, a presumed seizure pattern which was treated with intravenous paraldehyde. On the morning of April 16 Cheyne-Stokes respirations were observed and followed at 11 a.m. by cardiopulmonary arrest. Resuscitation measures were unsuccessful.

At no time during the admission did the child void. During the approximate 36 hours of hospital care, her temperature varied from 98° to 102°. Her weight was 8.85 kg. on admission and 8.9 kg. on April 16.

During the period of hospitalization the child was given one million units of aqueous penicillin and chlortetracycline 10 mg. intravenously every hour. She had nine doses of this preparation.

I wonder if we might see the x-rays, because I have some questions I would like to ask about them.

Dr. Leonard Langer**

The chest x-ray shows some patchy infiltrate at the right medial base. On the lateral film there appears to be some fluid in the major fissure adjacent to the infiltrate. An abdominal film taken early on April 15 shows some dilatation of small bowel loops. No colonic gas is visualized. This suggests a mild ileus of the paralytic type rather than a mechanical obstructive proc-

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*See Test Your Word Score Page 779.

**Assistant Professor, Department of Radiology, University of Minnesota.

ess. There is no evidence of ureteral reflux on the cystogram. However, on this film we do see an abnormal segment of colon. There are gross erosions of the colonic wall without any thickening of the wall of the dilated small bowel loop. The erosions seem to be limited to an area of transverse colon.

Dr. Good:

Although the protocol indicated that ulcerative colitis had been a consideration, we see no evidence of chronic disease of the colon. A more acute ulceration of the bowel seems a more likely possibility.

Our problem then is a 20-month-old child who had a respiratory infection and developed central nervous system symptoms which included confusion, disorientation and, several days later, seizures. The central nervous system manifestations were noted prior to fluid therapy. The child also had a history of pica. Then she developed bloody diarrhea and vomiting. The profuse vomiting was associated with hypertension, urinary shutdown, anuria, azotemia, and intestinal ulceration. In addition, the white blood cell count was 104,000.

Now, Dr. Langer, could you visualize the kidneys in any of your films, and could you estimate their size?

Dr. Langer

We see the kidney outlines reasonably well on the films. They don't appear grossly abnormal.

Dr. Good

I just wanted to be sure that the kidneys weren't extremely small or unusually large.

Poisoning

Certainly in a child with pica, we consider an intoxication as a basis for the damage to the central nervous system, to the kidney, and to the bowel. This combination of manifestations could be secondary to arsenic ingestion. In April in Minnesota it is possible to find rat poisons containing arsenic. Mercury is another possibility. No evidence was obtained of exposure to either of these compounds. This reassures me but does not lull me into complacency.

A few years ago we had a youngster who had apparently ingested a bismuth compound used in the treatment of warts. This child had a severe renal shutdown but no central nervous system or gastrointestinal disease. However, when I first began my pediatric studies at the Minneapolis General Hospital, two little children came in with central nervous system manifestations, drooping eyelids and severe gastrointestinal manifestations; and they rapidly developed anuria. Those children had ingested some rat poison that they had taken from the incinerator box in their apartment house. We finally made the correct diagnosis when their hair began to fall out. They were suffering from *thallium* intoxication.* This possibility must be kept in mind. Also, in April in Minnesota when car radiators are changed, a child, particularly an active child, who tends to

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*See Test Your Word Score Page 779.

Continued

put things in his mouth, might ingest sweet-smelling but non-nutritional substances such as anti-freeze, which can destroy the brain and kidneys. Ethylene glycol can produce a rapidly developing renal failure, as well as gastrointestinal and central nervous system manifestations. Poisoning, of course, is one of the common causes of morbidity and mortality in children and may appear as a bolt out of the blue in a child who has been vigorous and healthy.

Shigellosis

Also, with this combination of manifestations, one has to think very strongly of an infection from Shigella. This organism produces a potent neurotoxin and can, as a consequence, cause a very severe gastrointestinal upset with central nervous system symptoms. Renal damage is unusual but can occur with Shigella, especially with severe dehydration. Renal vein thrombosis occurs especially in young children who are dehydrated. Further, in a few case instances, bilateral cortical necrosis of the kidneys has been observed in patients with shigellosis. In this case the history about the defective water supply may be a clue. However, most shigellosis infections are transmitted by person-to-person contact.

The gastrointestinal manifestations of shigellosis occur after a short incubation period. It would be unusual to have central nervous system manifestations preceding gastrointestinal manifestations by the length of time intervening in this instance. The patients are usually febrile and show much toxicity. The toxicity was present here, but the temperature was normal. The stools were not like those usually observed in shigellosis, but again there is much variability, especially in small children. The diagnosis must be made, of course, by stool culture. The early onset of the central nervous system manifestations preceding the gastrointestinal symptoms, the lack of febrile course, and the atypical character of the stools make the diagnosis of shigellosis unlikely.

Acute Pyelonephritis

Acute pyelonephritis may present with primary gastrointestinal manifestations. With the acute toxicity there also may be convulsions and central nervous system disturbances. In a few of these patients the disease may be so fulminating as to produce the picture of renal shutdown. However, all of these things are associated with high fever, and she would have to have all the unusual manifestations of pyelonephritis in order to explain this case on that basis.

Chronic Renal Disease

In very young children, acute renal failure may follow respiratory tract infection or a gastrointestinal tract infection. Such a history may be observed, for example, with polycystic kidneys or in hypoplastic or dwarfed kidneys. These patients may limp along in borderline compensation, only to develop acute renal failure in the face of an acute infection.

Chronic nephritis with chronic nephropathy associated with obstructive uropathy can terminate with surprising suddenness after acute infection. The size of the kidneys makes dwarfed or polycystic kidneys an unlikely choice.

Cortical Necrosis

Bilateral cortical necrosis syndrome should be foremost in our minds. First of all, we have to explain this extremely high white count. Among the few conditions besides leukemia that can present in childhood with a high white count in the 50-100,000 range is bilateral cortical necrosis of the kidney. Bilateral cortical necrosis also may definitely occur as a consequence of gastrointestinal infections or be associated with gastrointestinal infections and also with convulsive disorders, as was pointed out by Zuelzer[1] et al. long ago. The gastrointestinal manifestations and the kidney disease could occur together here, with the primary disease probably being the gastrointestinal infection and the bilateral cortical necrosis secondary. Ulceration of the bowel may also be observed in this association.

Hemolytic Anemia-Uremia Syndrome

In 1955 Gasser[2] described a syndrome, of which there are now at least 50 case reports. I am speaking of the hemolytic anemia-uremia syndrome. One observes severe central nervous system disease, usually with convulsions, often with cyanosis, progressive anemia, (although the hemoglobin at the initial presentation in a few of the cases has been very close to the normal range), thrombocytopenia and rapidly developing renal insufficiency. The patients regularly present with vomiting or diarrhea which generally has been present from two to ten days and rapidly develop pallor, dehydration, convulsions, and hypertension. A few of them have petechiae. About 35% die with this syndrome, and bilateral cortical necrosis of the kidney has been present in some. The kidney in others shows a severe fulminating glomerulonephritis. The pathological picture may be like that seen in severe acute glomerulonephritis or subacute glomerulonephritis.

Hemolytic anemia is very interesting because it is usually a Coomb's negative hemolytic anemia. Few patients present jaundice. The peripheral smear shows red blood cells with fragmentation, poikilocytosis* and acanthrocytosis.* Especially significant in light of our patient today was the case reported by Shumway and Miller[3]. In this case the hemolytic anemia and the renal disease were *dissociated* in one episode and *associated* in another episode in the same patient. That is to say, the patient presented one episode where an intimate association of the hemolytic anemia and the uremia was observed; and another in which the glomerulonephritis was present without the hemolytic anemia, and then later the hemolytic anemia again developed.

Moschocowitz Syndrome

A final possibility is primary thrombotic thrombocytopenic purpura or Moschocowitz's syndrome. I am not sure how well the bilateral cortical necrosis of the kidneys and the hemolytic anemia-uremia syndrome of Gasser can be separated from thrombotic thrombocytopenic purpura. At least, pathologically, most of the cases do not show an overlap.

In thrombotic thrombocytopenic purpura, the primary material being deposited peripherally in the small arterioles consists of clumps of platelets entrapped in fibrinoid material or even fibrin. The lesions may involve the small arterioles or the arteriolar side of the capillary circulation. Certainly this disease is rare in young children. It has, however, been described, and we have observed a couple of cases. In a few instances classical thrombotic

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*See Test Your Word Score Page 779.

Continued

thrombocytopenic purpura may be the initial manifestation of lupus erythematosus. This pathologic process certainly can produce a combination of severe gastrointestinal disease, severe, rapidly progressive renal disease, and severe nervous system disease, all of which were present in our patient.

The syndrome of Gasser, the hemolytic anemia-uremia, is the most common of the severe, rapidly destructive diseases in children. All this patient's manifestations would be compatible with this possibility. The admission hemoglobin of 11.6 is the red flag against this diagnosis and favors bilateral cortical necrosis of the kidney with gram-negative bacterial sepsis. I favor this latter diagnostic possibility. On either basis what we will likely see at autopsy is bilateral cortical necrosis of the kidney as a reflection of the more generalized vascular disease. In the hemolytic anemia-uremia syndrome, which usually occurs in children of under one year or in older children, the glomeruli of the kidney are loaded with gamma globulin deposits.

Gamma Globulin Deposits

How do these gamma globulin deposits occur? I think the best bet, although nobody knows the mechanisms of the hemolytic anemia-uremia syndrome, is antigen-antibody complexes form from exogenous antigen and an antibody being produced in the body. The hemolytic anemia and renal disease are not necessarily dependent upon one another. Peter Miescher has shown clearly that antigen-antibody complexes have a selective affinity for red blood cells, which can act as innocent bystanders in receiving toxic soluble antigen antibody complexes from the circulation. These attach to red cells by a process known as immune adsorption, render the red cells abnormal and lead to their rapid destruction.

Shulman has demonstrated the same pathogenetic basis of thrombocytopenia in some cases of drug-induced thrombopenia. Dixon and his coworkers have shown clearly that the kidney also may function as an innocent bystander in immunological disease and can be the subject of assault by these same toxic, soluble antigen-antibody complexes. In light of the Shumway-Miller case, the best consideration of the pathogenetic mechanisms in this disease is that you have both of these systems: red blood cells and kidneys receptive of damage from such a source, sometimes together — sometimes separately.

Soluble Antigen-Antibody Complexes

Shulman also has recently shown that platelets may be damaged, not by a direct attack of the immunological mechanism on the platelets, as in auto-immunity, but by an attack of the soluble antigen-antibody complexes attacking the platelets again as innocent bystanders and producing damage to these cells. So I think we will find gastrointestinal inflammatory disease with ulceration on the postmortem. Although this may be an underlying chronic process, I think it is acute. At least the x-rays suggest this was the case. I would expect there would be evidence of vasculitis in the bowel and perhaps acute necrotizing vasculitis. I recently saw a case in St. Louis with exactly the same syndrome, in which the bowel was involved in a clearly destructive vasculitis which had apparently preceded by some considerable period the development of the renal disease and bilateral cortical necrosis of the kidneys.

Multiple Kidney Lesions

In the kidneys we could have any of several lesions. We could have a true bilateral cortical necrosis, bilateral renal necrosis without limitation to the cortex, or we could have severe acute glomerulonephritis or subacute glomerulonephritis with marked endothelial proliferation. Because of the very high white count, I expect to find bilateral cortical necrosis of the kidneys with deposits of hyalin fibrinoid material in the kidney, just as we see in the generalized Shwartzman reaction in the rabbits Dr. Thomas and I studied so intensively here a few years ago.

Central Nervous System

So far as I am aware, the central nervous system has not been well studied in the hemolytic anemia-uremia syndrome. If this is related to the other pathogenetic mechanisms, I would presume that the central nervous system manifestations would be the result of a destructive occlusive vasculitis — a consequence of intravascular coagulation. I do not attribute the central nervous system manifestations in this child entirely to the water intoxication which I think she had to some degree. The latter may have been contributory to the expression of central nervous system abnormalities but was not primary. Rather, I think this child was loaded with water at the time and could not deal with the fluid, and this may have contributed to the convulsions; but I think the central nervous system disease, as seems clear from our history, antedates the production of a low sodium state. This, then, is my analysis of this patient!

Dr. Good's Diagnosis: Bilateral Cortical Necrosis of the Kidneys

Dr. William Krivit*

Hemolysis can cause an elevated white cell count. But the amount of hemolysis was slight, as the hemoglobin was stable and there was no evident jaundice. Bleeding can also cause leucocytosis. But I wonder whether or not the white blood count of 104,000 might more properly relate to an infectious process such as shigellosis.

Dr. Good

The only infections that I am familiar with that alone will produce a white count of this sort are severe generalized septicemias with extensive peritoneal involvement or pertussis. Pertussis is always associated with a lymphocytosis but is not common. In bilateral cortical necrosis of the kidney, even without a hemolytic anemia, very marked elevation in the white count occurs. We frequently produce bilateral cortical necrosis of the kidney in our rabbits over in the laboratories through the agency of generalized Shwartzman's reaction. The white count of hemolytic anemia-uremia syndrome is sometimes in the 40,000 to 60,000 range. I found none yet reported as high as 104,000.

Dr. Joseph St. Geme**

Attempts to isolate Salmonella or Shigella from several fecal specimens and from a piece of bowel obtained at postmortem were unsuccessful. Multiple cultures of the blood were also negative, as well as cultures of

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the spinal fluid, pericardial fluid and peritoneal fluid. The only microbiologic recovery, and I don't think it is significant, was an adeno-virus type I, which is usually a nonpathogen, frequently prevalent in the community, and which was also present in the feces of another child on the ward at the same time. This virus was recovered from a piece of bowel.

Dr. Robert Ulstrom*

The probabilities of this being an acute poisoning in this child are so great that it would be urgent to determine what the poison was. Some heavy metal poisons do have specific antidotes which can be administered even relatively late after the acute poisoning.

Dr. Good

I would certainly agree on the combination of manifestations in a child with pica. However, intoxication doesn't usually give this high a white count, and I placed it low on the list. We should always, in a patient like this, be exhaustive in our search for a toxic agent. We may uncover something that can be manipulated to the benefit of our patient.

Postmortem Findings

Dr. Stanley Stark**

Toxicology specimens were taken, but they were not sent to the proper laboratory. There was 20 cc. of clear yellow fluid in each pleural cavity and 10 cc. of serosanguineous fluid within the peritoneal cavity. Frank peritonitis was absent on gross inspection. The heart and lungs appeared grossly normal. Their weights were normal. The most striking finding was seen in the large bowel. Starting about five centimeters proximal to the iliocecal

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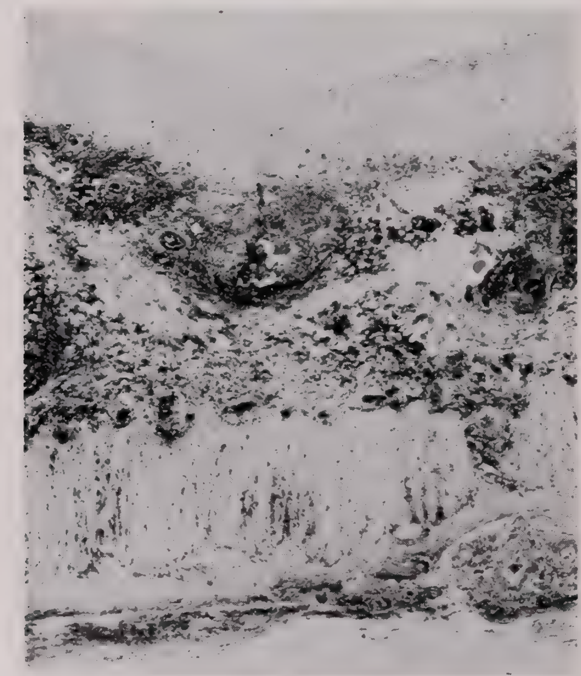

Fig. 1 — This shows extensive necrosis of most of the wall of the colon. There is some sparing of the smooth muscle in the outer portions of the colon wall. x35

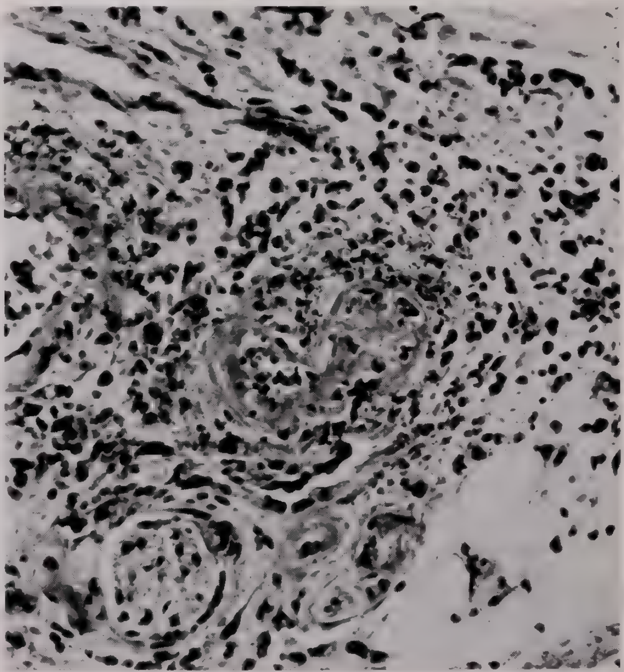

Fig. 2 — This shows necrosis and inflammation in the small vessels in the wall of the colon. x450

valve and extending to the rectum, the bowel had a very striking red-brown color. Even the appendix was involved. When the bowel was opened, there was brown-red debris on the mucosal surface.

The kidneys were of normal weight for the child's age, but grossly had a very swollen appearance. They were deep brown-red in color and, when cut, the kidney tissue actually bulged forth. The color of the cortex was brown-red with several pale foci 1-2 mm. in diameter. The large vessels of the bowel and kidney were traced and were patent and normal.

Dr. Barbara Burke*

The most interesting microscopic findings were those of the colon and the kidneys. There was extensive necrosis of most of the wall of the colon in the areas sectioned. The degree of necrosis and the extent of inflammatory reaction were marked in the mucosa. There was minimal serosal involvement. Viable smooth muscle was identified in the outer portions of the muscular layer (Figure 1). There was thrombosis in several of the vessels and an extensive inflammatory reaction in the vessel walls (Figure 2). Whether this lesion began as an inflammatory reaction, with involvement of vessel walls, thrombosis, and extensive necrosis, or whether a vasculitis was present as the primary lesion is a difficult question. Unfortunately we were unable to culture any organisms usually responsible for this kind of colonic lesion. Intravenous broad spectrum antibiotics were given during hospitalization which may have altered the bacteriology report. There was bilateral renal cortical necrosis and, as usual, there was sparing of the glomeruli in the corticomedullary junction as well as those immediately beneath the capsule. There was thrombonecrosis of afferent arterioles and glomerular capillaries with bright pink fibrinoid material occluding these vessels (Figure 3).

The patient also had minimal acute bronchopneumonia and a minimal but definite acute inflammatory reaction in the leptomeninges of the cere-

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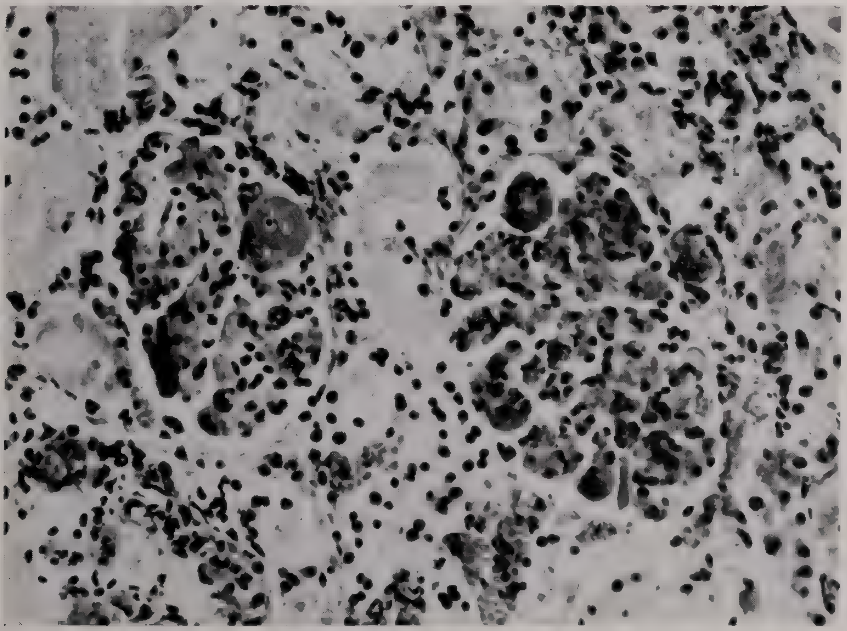

Fig. 3 — This shows deposition of fibrinoid material and early necrosis in the glomerular capillaries. x450

Continued

bral cortex and the cerebellum. Perhaps these lesions were the result of terminal seeding of the blood stream with bacteria. We found no vasculitis in any other organ, and the brain was otherwise entirely normal.

The most likely diagnosis is bilateral renal cortical necrosis, the result of gram-negative bacteremia with terminal pneumonitis and meningitis. The portal of entry for the gram-negative organism may have been the colon, and the disease may have begun as a dysentery.

The usual poisons capable of producing renal cortical necrosis do not seem likely, because of lack of associated lesions in other organs, particularly the liver. Poisons capable of producing necrotic lesions of the gastrointestinal tract do not usually cause renal cortical necrosis but often do cause hepatic and other organ involvement not found in this child. Without a toxicology study, however, we cannot definitely exclude the possibility of poison.

Dr. Good:

I saw two cases in an epidemic pathogenic E coli diarrhea in an army post in Utah which ended in the same way. It doesn't necessarily have to be Shigella infection but can be due to other gram-negative bacteria.

It would be informative to know whether or not immunohistochemical studies would reveal the occluding material to be primarily fibrinogen or primarily gamma globulin. In the hemolytic anemia-uremia syndrome the primary material occluding the vessels appears to be gamma globulin. Fibrinogen is not present here. In the generalized Shwartzman reaction the occluding material is entirely fibrin or fibrinogen.

David Duffell, M.D.*
University of Minnesota

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*Department of Pathology.

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Early Man Vindicated?

A toad boiled in water, made into a mess like the witch's caldron of Macbeth and given to a man swollen with dropsy, seemed to benefit him. Pure fancy? That is what scientists thought until a few years ago when they discovered that the toad has in its skin a drug called bufonin that may actually be helpful in treating dropsy.

From ancient China came the belief that eating bits of dragons' bones drove away the evil spirit that caused babies to have fits. Foolish as this sounds, dragons' bones were really those of dinosaurs buried in the sands of the Gobi Desert. Today for a certain kind of convulsion that babies may have the doctor prescribes calcium, and the dinosaur bones, like all others, contain calcium!

Would you believe that the ashes from a burnt sponge could help relieve a swelling in the neck? Ashes were used, and they drove away the spirit that caused the swelling — according to the ancient theory. Modern science has shown that a swelling of the neck called a goiter may occur when there is too little iodine in the food and drinking water, as is the case in some parts of our country. Small amounts of iodine are given to prevent goiter. The ashes of sponge contain iodine.

— Haggard, Howard W.: The Doctor in History, Yale Univ. Press, 1934.

Grand Rounds

The Gastrointestinal Manifestations of Scleroderma[*]

NEIL HOFFMAN, M.D.
Medical Resident

> *"To wither slowly, and to be beaten down, marred and wasted until one is literally a mummy incased in an ever shrinking, slowly contracting, skin of steel. . . ." — Sir William Osler*

SCLERODERMA IS a generalized disease of connective tissue involving the skin and various viscera. It was first described by Curzio in 1752 and was recognized as a primary skin disorder.[1] The term scleroderma means "hard skin". Only recently have the systemic manifestations of this disease been recognized. Heredity is not considered significant. Females seem to be involved over males by about 3:1, and adults are usually affected.[1,2] Most cases fall between the ages of 20 to 50, while the highest incidence is noted between 51 to 60 years of age.[1] Early symptoms include swelling and stiffness of the skin, joint tenderness, dysphagia, and vague abdominal complaints.[1,2] There may be hyperpigmentation surrounding the involved skin areas. Articular symptoms are common early in the disease.[3] Sclerosis usually begins in the hands and then spreads to the face and forearms.

Clinical Stages[4]

Edematous (Table 1)

In this stage the skin is tense but appears swollen. It does not pit on pressure, and cannot be folded. Due to the tautness or loss of elasticity, the face assumes a fixed or mask-like expression.

Indurative

In this stage the skin is stiff and firm, as best seen on the fingers. There may be flexion contractures at the fingers, due to tightening of the skin. Hyperpigmentation may be present.

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[*] Presented as a Medical Grand Rounds at Hennepin County General Hospital, Minneapolis, January 18, 1966.

Continued

TABLE 1*

Cutaneous Manifestations of Scleroderma
Series of 727 Patients

Finding	Percent of Patients
Sclerosis	100
Ulceration	35.4
Pigmentation	30.5
Edema	23.9
Telangiectasia	18.9
Calcinosis	8.9

*From Winkelmann: Arch Derm 84, 1961.

Atrophic

In this stage the finger tips become small and pointed. Mucous membranes become dry and are in part replaced by collagen. Ulcers may develop on these areas, secondary to ischemia and increased tension.

While it seems, in many cases, that scleroderma is confined to the skin, there tends to be a rapid, progressive, systemic involvement that may lead to death, usually from cardiac or renal failure.[5] Due to the generalized involvement of this disease, Goetz[6] in 1945 proposed the more descriptive term, "progressive systemic sclerosis".

Etiology

There have been numerous attempts to establish an etiology for this disease; but though many have been proposed, there is as yet no proof of the cause of scleroderma.

Infection

Scleroderma has been reported following various infections. Tonsillitis, scarlet fever, diphtheria, pneumonia, syphilis and tuberculosis have all been considered responsible.[1] O'Leary[7] thought scleroderma was due to arsenic intoxication, as he noted increased arsenic excretion in the urine of several patients with the disease.

Endocrine

The entire endocrine system has at one time been suspected in the etiology of this disease. Thyroid dysfunction was thought to be important; but O'Leary,[7] in over 150 cases, showed 97 per cent to have normal thyroid function tests. Desiccated thyroid seems to have no effect on the progression of the disease. The parathyroid glands have been suspected because of the calcium deposits that are seen in the skin ulcers; but surgical removal of these glands seems to have no effect on the disease process.[1]

Neurogenic

A neurogenic basis for scleroderma has been suspected because of Raynaud's phenomenon, frequently seen in people with cutaneous scleroderma. Degenerative changes have been noted in the sympathetic nerve fibers in the skin, often preceding any collagen disturbances.[2] Although Raynaud's disease is frequently an early finding in scleroderma, there has been no proven relationship. O'Leary[7] reports that 50 per cent of scleroderma starts as arthritis or as a vasospastic phenomenon (Raynaud's).

Allergy

The allergy theory has never become popular, but there have been new cases of scleroderma following vaccination. Also, there generally is an increase in gamma globulins in scleroderma.[2,7] Walder[8] reports a series of seven patients manifesting symptoms of scleroderma following contact with various organic solvents. There are no specific laboratory findings in the disease; rather they reflect the involvement of various organic systems.

There has been an attempt to classify as a separate disease called acrosclerosis those cases that exhibit Raynaud's phenomenon and cutaneous involvement of the hands and face. Goetz,[6] however, has shown that both scleroderma and acrosclerosis represent a spectrum of only one disease, progressive systemic sclerosis (scleroderma), which may present with a variety of symptoms and manifestations.

Gastrointestinal Involvement

Scleroderma can no longer be classified as a dermatologic disease. Reports have recently been published pointing out the generalized nature of this disease. Autopsy series show the gastrointestinal tract to be involved in about 60 per cent of those individuals having cutaneous manifestations of scleroderma.[9,10,11] The symptoms of gastrointestinal involvement may follow the onset of cutaneous findings from a few months to twenty years.[9,10] Recently reports of gastrointestinal involvement before the onset of cutaneous manifestations have been noted.[4] About 10 per cent of patients with scleroderma show signs of visceral involvement without any cutaneous manifestations.[13] Herrington[12] reports on a patient who presented with symptoms of incomplete obstruction for six years. In this case laparotomy was finally resorted to, establishing the diagnosis of scleroderma. Some four and one-half years following surgery, there was still no evidence of cutaneous manifestations of scleroderma.

Esophagus

Ehrman, in 1903, reported the first case of scleroderma associated with esophageal abnormalities.[13] His patient presented with symptoms of progressive dysphagia. Esophagoscopy showed redness of the mucosa, with generalized thickening and edema. There was scar tissue, with constrictive bands and ulcerations about the lower half of the esophagus.

Esophageal involvement with scleroderma usually produces symptoms of *progressive dysphagia,* first with solid foods, then with liquids. There may be a feeling of fullness after swallowing, or there may be a burning sensation in the epigastric area unrelated to swallowing. Nausea is commonly present. There may also be, as a complicating factor, difficulty in mastication, due to the inability to fully open the mouth.[1,2,10] Such esophageal involvement, when an early manifestation of scleroderma, may unfortunately be disregarded by the physician as a functional complaint.

Some 45 to 90 per cent of patients with scleroderma show changes on x-ray.[10,14,15] The earliest radiographic findings seem to be *diminished*

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peristaltic waves in the esophagus.[27] To appreciate this one should examine the patient in the recumbent position to negate the effects of gravity on the barium meal. Dornhurst[16] has found that by this method one can detect esophageal involvement before clinical symptoms are evident. The primary peristaltic wave normally travels the entire length of the esophagus during deglutition; however, in scleroderma it descends only to about the suprasternal notch.[11,23,30] Cinefluoroscopy shows a *prolonged transit time,* with slight dilatation of the esophagus, but there is usually no evidence of complete obstruction in the esophagus.[13] Food has been noted to remain in the esophagus for more than one hour while the patient is recumbent, but when he assumes an erect position normal rapid transit time is observed. Emptying of the esophagus may depend entirely on gravity.[30] By measuring esophageal pressures, one finds the upper half of the esophagus to have normal contractions and normal transit time, whereas the contractions become feeble or absent in the lower half of the esophagus.[2] There is then a loss of pressure gradient across the cardio-esophageal junction, resulting in reflux of gastric contents, causing esophagitis.[9]

Areas of constriction usually appear a few centimeters above the cardio-esophageal junction, with proximal dilatation of the esophagus.[2,11] (See Figure 1.) Occasionally this picture may be mistaken for achalasia or cardiospasm, the difference being that in scleroderma the lower one third of the esophagus is involved, whereas in cardiospasm, usually only the cardia is involved.

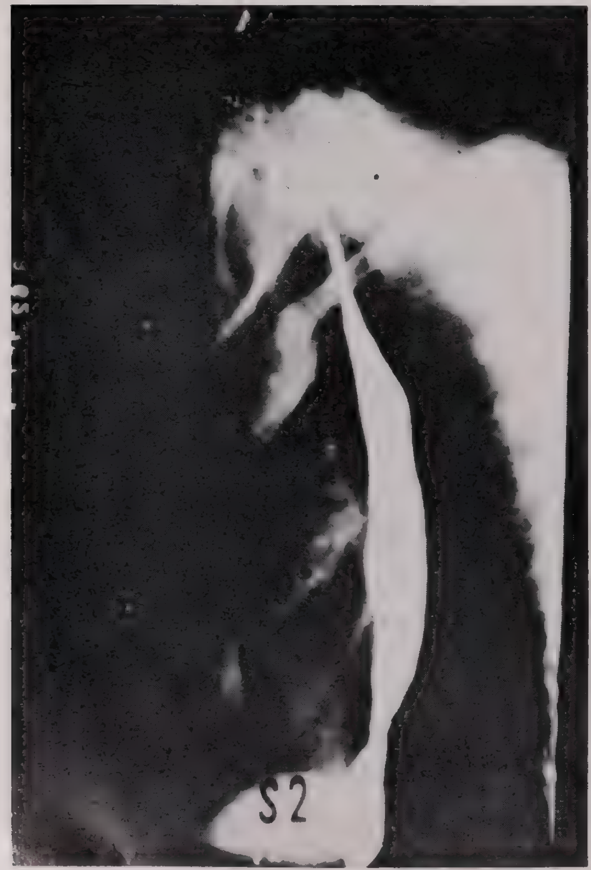

Fig. 1 — X ray # 1.

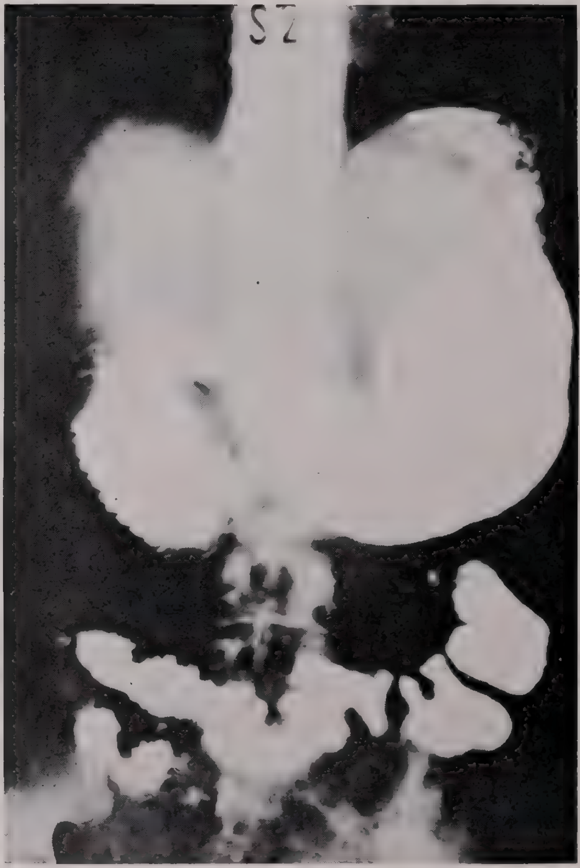

Fig. 2 — X ray # 2.

Pathology

A patchy deposition of an acellular collagenous fibrous tissue has been reported in the submucosal, muscular, and serosal layers.[9,28] It is this deposition that produces the stricture in the lower esophagus, as seen on x-ray, causing rigidity of the lower esophagus with resultant reflux.[4,17] Goetz,[6] in an extensive study, reports one patient who developed a niche at the constricted portion of the esophagus and succumbed. Autopsy showed the submucosa was thickened, with acute and chronic inflammation. He concludes therefore that sclerosis of the connective tissue is a basic feature of this disease process and produces many of the esophageal symptoms. Anderson[18] substantiates this and feels that the resultant atrophy of the muscular layer is likewise a basic pathologic process of esophageal involvement in scleroderma. Also there is a collagenous degeneration of the submucosa. The mesenteric and submucosal ganglia do not appear to be involved, although atrophy of adjacent structures may make them more prominent. Vascular changes of varying degrees may also be present.[6,9,20] One may see mucosal ulcerations, hiatal hernia, or erosions in association with scleroderma; but esophageal perforation is rare.

Stomach

There have been no reported lesions of the stomach with scleroderma.[1] Rake[17] reports dilatation and lymphocytic infiltration in the mucosa, with delay in emptying and spasm in the antral area.[20] Wolfel[21] reports one case that seems to affect the stomach primarily. His patient had narrowing of the gastric antrum that radiographically resembled linitis plastica. Hoerner[15] undertook a study to relate common gastrointestinal diseases to scleroderma. In a review of 724 cases only four per cent had peptic ulcer disease associated with visceral scleroderma. The incidence of peptic ulcer in the general population runs five to ten per cent. Piper,[10] in a series of 31 patients, reported two gastric ulcers. Unlike dermatomyositis, where malignancy is reported to be as high as 20 per cent, there appears to be no increased evidence of gastrointestinal malignancy in scleroderma.[9]

Small Bowel (Tables 2 and 3)

Scleroderma involvement of the small bowel may be more common than was previously thought. There may be small bowel involvement in the absence of esophageal or other visceral involvement.

Recognition of small bowel involvement in scleroderma is relatively recent. In 1962 there were only 67 reported cases, including one by Reinhardt in which 33 cases were reported.[22] Malabsorption seems to be a dominant feature in scleroderma of the small bowel but occurs late in the disease.[5,9,31] Factors causing malabsorption are not well known. There have been reported mucosal infiltration of round cells, as seen in sprue, and these are thought to alter the absorptive capacity of the bowel. Scleroderma can also present as obstruction. Herrington[12] reports a successful result with surgery in a case of scleroderma with small bowel involvement.

Forty-four per cent of patients with scleroderma have small bowel abnormalities,[22] with the duodenum usually involved. The duodenal bulb dilates and retains barium long after the stomach empties. There has been retained barium in the duodenal bulb for as long as 24 hours after ingestion.[6,22,23] (See Figure 2.) Large dilated loops may mimic intestinal obstruc-

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tion. Dilatation of the second and third portion of the duodenum is quite constant in scleroderma.[23] In the jejunum there seems to be flocculation of barium as well as isolated dilated loops. The mucosa is thickened and irregular, and there is delayed transit time through the small bowel.[22] Reinhardt has found small bowel involvement in the absence of esophageal findings (Table 4).

Microscopic Pathology

As in parts of the gastrointestinal tract, so there is atrophy also of the muscle layers with irregular replacement by collagen fibers. The villi are atrophic. Haskins[9] describes a "ceroid" pigmentation in the smooth muscle, the significance of which is not known, but which is thought to represent a vitamin E deficiency, probably secondary to malabsorption. Rossom[24] did peroral duodenal biopsies in six patients with scleroderma and found that Brunner's glands were incased in collagen and that the muscular elements were atrophied and fragmented. The glands themselves were

TABLE 2*

Small Bowel Changes in Scleroderma

Abnormality	No. of Cases
1. Dilatation and retention of barium in the duodenal loop, sometimes as long as 24 hours.	11
2. Flocculation and segmentation of barium in the duodenal loop.	9
3. Dilatation and retention of barium in the duodenal bulb.	7
4. Dilatation of loops of small bowel in the jejunum or ileum.	7
5. Thickening and irregularity of the mucosa in the small bowel.	7
6. Delayed transit time.	5
7. Dilatation and atony of stomach.	3
8. Partial small bowel obstruction.	1

*From Reinhardt: Amer J Roentgenol 88, 1962.

TABLE 3*

Small Bowel Involvement

Case No.	Age	Race	Sex	Raynaud's Phenomenon	Skin Biopsy	Esophageal Motility	Duodenal Biopsy	Small Bowel X-Ray
1	54	W	M	Absent	+	Abnormal	4+	Abnormal
2	34	N	F	Present	+	Normal	4+	Normal
3	41	W	M	Present	+	Abnormal	0	Normal
4	43	N	F	Present	+	Abnormal	3+	Abnormal
5	53	W	F	Present	+	Abnormal	1+	Abnormal
6	42	W	F	Present	Not done	Abnormal	0	Normal
7	71	W	F	Present	+	Abnormal	1+	Normal
8	32	W	F	Absent	(-)	Abnormal	2+	Normal

*From Rosson: New Engl J Med 272, 1965.

TABLE 4

Experience with Scleroderma at Hennepin County General Hospital
1956 - 1965

No.	Patient	Age	Race	Sex	Raynaud's Phenomenon	Skin Biopsy	Esophageal Abnormalities	Small Bowel X-Ray
1	B.B.	35	N	F	Yes	No	Yes	Not done
2	B.D.	43	W	M	Yes	Yes	No	Not done
3	T.S.	45	W	F	Yes	Yes	Yes	Yes
4	M.D.	73	W	F	No	Equivocal	Yes	Decreased motility
5	L.N.	61	W	F	Yes	Yes	Yes	Negative
6	F.B.	54	W	F	No	Negative	Yes	Negative

normal, the deposition of collagen around them probably occurring early in the disease.

Large Bowel

Involvement of the colon by scleroderma produces decrease in motility. The colon may become atonic and constipation may occur.[9,11] Radiographically, there may be loss of haustral markings, shortening of the involved bowel, and a picture similar to ulcerative colitis. Heinz[23] reports that 53 per cent of patients with large bowel involvement have diverticula, differing, however, from the normal colonic diverticula which are globular in appearance and have narrow stalks. The diverticula seen in scleroderma are saccular, wide-mouthed, and occur mainly in the transverse colon. These patients seem to tolerate surgery poorly and the mortality with resection is high. Cullinan[26] describes the sigmoidoscopic changes as showing pale, dry mucosa. Only rarely does the mucosa undergo ulceration; but when it does occur, it is thought to be the result of ischemia rather than of infiltration and sclerosis.

Liver

The liver is rarely reported as being involved in scleroderma. One series,[27] however, comprises 727 patients, eight of whom had signs of hepatitis. Liver biopsy shows changes resembling post-necrotic cirrhosis.

Experience at Hennepin County General Hospital (Table 4)

During the ten-year period, 1954 to 1965, there have been six new cases of scleroderma diagnosed at this hospital. Our incidence of females to males is 5:1, in comparison to 3:1 in most series. Four of our patients had symptoms in their extremities compatible with Raynaud's disease; five had dysphagia, with radiographic abnormalities suggesting scleroderma. Only one patient had small bowel involvement on x-ray, consisting of dilatation of the second and third portion of the duodenum, as well as dilated areas of the jejunum, with an abnormal mucosal pattern. We have had no cases in which the gastrointestinal manifestations preceded cutaneous involvement. This is probably due to a low suspicion of the visceral aspects of this disease. One must examine patients with visceral complaints that include dysphagia, in the recumbent position; otherwise, early cases of scleroderma

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will be missed. The decrease or loss of peristaltic activity in the lower esophagus should make one suspect scleroderma.

Treatment

As of now, there is no satisfactory treatment for scleroderma. Therapy has generally been disappointing, because we do not know the etiologic basis for this disease or understand fully all of its manifestations. Past treatment has included thyroidectomy, parathyroidectomy, sympathectomy, x-ray, ultra sound, posterior pituitary extract, antibiotics, antisyphilitic agents, vitamins, chelating agents, and steroids.[9,14,23] Also symptomatic treatment for the gastrointestinal symptoms has been used. Urecholine may be beneficial in selected cases where motility is bothersome. Evans reports relief of dysphagia by thoracic sympathectomy; but the x-ray picture remains the same following surgery. Steroids have generally proved disappointing. They seem to be more effective in managing the articular and cutaneous manifestations.

Summary

Scleroderma should be thought of as a disease affecting many organ systems with protean manifestations. Probably the term proposed by Goetz, of progressive systemic sclerosis, is a more meaningful term and should be used in discussing this entity. Symptoms depend on the tissues involved. The disease process may be fulminant or remain in an arrested state. Its course is usually marked by periods of exacerbations and remissions. There is no curative therapy. Symptomatic treatment is beneficial. Steroids seem to have some value but are most effective on the articular manifestations.

Case Report

A 45-year-old white female first came to this hospital in 1959. At that time she had mild cutaneous involvement about the hands and a two-week history of dysphagia. Skin biopsy was done, the results being compatible with scleroderma. Previous hospitalization included a ruptured appendix and Lannec's cirrhosis. Her course has been stable with episodic exacerbations of her disease.

She was hospitalized in April 1965, with progressive dysphagia, arthritis, and vasospastic changes in the upper extremities. The skin over her hands, face, and neck was taut, smooth, and velvety. Her liver was enlarged three to four centimeters below the costal margin. She had metacarpal swelling, with marked ulnar deviation of both hands. The deep tendon reflexes showed a prolonged relaxation phase.

Laboratory Data

X-Ray: An upper G.I. series, taken on April 23 1965, shows a stricture in the distal esophagus, with lack of peristaltic activity. The stomach and duodenum were moderately dilated, and there was loss of the normal jejunal mucosal pattern. A barium enema showed diverticula in the mid portion of the descending colon.

ECG. was normal. L.E. prep was normal on three different determinations. PBI. was 4.9 micrograms per cent. BUN. creatinine, BSP. and the Papanicolaou's smear were within normal limits. F.A.N.A. was positive in a 1:10 dilution.

She was treated symptomatically with partial remission of her symptoms.

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7-31 May be secured from the Grand Rounds Editor.

Do not continue eating until the belly is distended. — Maimonides (12th century)

Advances

Antibacterial Management of Infections Due to Gram-Negative Bacilli[*]

Part I. Introduction, Pathogens, and Use of Streptomycin, Dihydrostreptomycin, Neomycin, Kanamycin and Gentamicin

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EXPERIENCES WITH infections due to gram-negative bacilli have been reported periodically by members of our group. During the last 25 years, an increasing incidence of serious infections due to these bacilli has been observed.[1-9] With the availability of effective antibacterial agents, greater effort is expended at diagnosing these infections, but one hesitates to attribute the increase to this alone. Perhaps of more significance is the emergence of an expanding group of individuals susceptible or predisposed to infection due to gram-negative bacilli. In this regard, antimicrobial control of other infections that formerly caused death may have preserved more candidates for ultimate invasion by gram-negative bacilli. Also, there are diseases of increased incidence in an aging population, such as diabetes mellitus, malignant neoplasms, and cirrhosis, which possibly predispose to gram-negative bacillary infections. In addition, there are modern therapies that prolong life in patients with limited ability to resist infection, and some, such as adrenal glucocorticoids, radiation, and radiomimetic therapy as well as antimicrobial therapy itself, that may alter or bypass defense mechanisms of the host. An important pathogenic factor appears to be the use of surgical and instrumental procedures whereby invasion with gram-negative bacilli is facilitated. It is evident that multiple factors may be involved in the increasing incidence of these infections.

Pathogens

Among the gram-negative microorganisms, there are the gram-negative bacilli. When one concerns himself solely with the latter bacteria, he thereby excludes from consideration the group of cocci referred to as Neisseria (Table 1). He also removes from consideration the spirochetes or spiral microorganisms which, while often difficult to stain by the Gram method, are usually gram-negative when they accept the stain. Also excluded are the *Mycoplasma* and *Rickettsia.* As a therapeutic consideration, infection due to Neisseria and spirochetes or spiral microorganisms are generally managed with such antimicrobial agents as penicillin, employed against gram-positive cocci. However, in pneumonitis due to *Mycoplasma pneumoniae* or in rickettsial infections, one uses antimicrobial agents such as a tetracycline, which are often employed against gram-negative bacilli.

Also in restricting a discussion to gram-

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[*] The six parts of this paper were presented, in part, at the Symposium on Antibacterial Agents sponsored by the Southern California Society of Hospital Pharmacists, Los Angeles, California, May 2, 1965.

[**] Mayo Clinic and Mayo Foundation: Section of Medicine.

negative bacilli, one obviously excludes from consideration the gram-positive bacilli. Infections due to organisms of Mycobacterium require rather specialized therapeutic regimens, but the management of tuberculosis includes the use of streptomycin, which is employed against gram-negative bacilli. Antimicrobial agents, such as penicillin, which are often employed against gram-positive cocci, have been effective in cases of gas gangrene, diphtheria, anthrax, listeriosis, and erysipeloid. *Lactobacillus* and *Bacillus subtilis* organisms rarely warrant therapeutic consideration.

Excluding gram-negative microorganisms other than bacilli and gram-positive bacilli from our discussion, the major "gram-negative bacilli" can be considered (Table 2). Among the Enterobacteriaceae are the coliform bacilli which include *Escherichia coli,* the *Klebsiella-Aerobacter-Serratia* group and the *Paracolobactrum* or paracolon bacilli. In addition to the coliform bacilli, organisms of *Proteus, Alcaligenes, Salmonella,* and *Shigella* also occur in the intestinal tract. The use of intravenously administered penicillin G in doses of 20 to 60,000,000 units/day has been suggested in infections due to Enterobacteriaceae, excepting *Proteus* organisms. *P. mirabilis* may be sensitive to more orthodox penicillin dosage, whereas *Proteus* organisms that are indole-producing *(P. vulgaris, P. rettgeri, P. morganii)* are resistant to even such a heroic dose. In patients allergic to penicillin who have infections due to *P. mirabilis,* other drugs which may be considered include erythromycin and novobiocin. Because other effective drugs are available, there probably is no need of frequent penicillin therapy for infections due to Enterobacteriaceae, except for some of those due to *P. mirabilis.* In this regard, massive doses of penicillin have been recommended in the management of carriers of *S. typhosa.* Of the Enterobacteriaceae, *E. coli, Klebsiella-Aerobacter,* and *Proteus* organisms are encountered most often in routine medical practice.

Pseudomonas organisms and members of the Bacteroidaceae may have enteric residence but are not classified as Enterobacteriaceae. Polymyxin B or colistin is employed in serious infections due to *Pseudomonas* organisms, and such bacilli are vir-

TABLE 1

Some Microorganisms to be Distinguished
From the Gram-Negative Bacilli

Gram-negative microorganisms other than bacilli
1. *Neisseria*
   - *N. meningitidis*
   - *N. gonorrhoeae*
   - *N. flavescens* (pigmented, rarely causes meningitis or endocarditis)
   - *N. catarrhalis* } (members of respiratory flora)
   - *N. sicca* }
2. Spirochetes or spiral microorganisms:
   Treponema pallidum, *Spirillum minus*, *Leptospira*
3. *Mycoplasma* (PPLO)
4. *Rickettsia*

Gram-positive bacilli
1. *Mycobacterium*
2. *Clostridium*
3. *Corynebacterium*
4. *Bacillus anthracis*
5. *Listeria monocytogenes*
6. *Erysipelothrix insidiosa*
7. *Lactobacillus*: *L. acidophilus* (Moro's bacillus)
   N.B. Boas-Oppler bacillus (of gut) and Döderlein's bacillus (of vagina)
8. *Bacillus subtilis* (member of skin flora, rarely pathogenic)

tually always sensitive to these toxic drugs; however, sometimes *Pseudomonas* organisms are sensitive to other drugs such as streptomycin, the tetracyclines, and the sulfonamides, which may have use if the clinical situation and the in-vitro data allow. As a therapeutic consideration, a tetracycline is preferred in the management of serious infections, such as bacteremia due to *Bacillus fragilis* or the necrobacilli. However, in infections due to fusospirochetes and in the bacillary form of rat-bite fever and Haverhill fever, which are caused by *Streptobacillus moniliformis,* penicillin is recommended. The fusospirochetal diseases include gingivostomatitis (trench mouth), pharyngitis (Vincent's angina), vulvovaginitis or balanitis, lung abscess which may progress to pulmonary gangrene, and rarely bacteremia.

Infections such as brucellosis, plague, and tularemia respond to streptomycin and to a tetracycline but, in infections due to *Pasteurella multocida,* penicillin is preferred.

Among the members of the *Haemophilus* genus, *H. influenzae* is a cause of meningitis, otitis, mastoiditis, endocarditis, and pneumonia, which may be primary or secondary to viral disease. *H. parainfluenzae* and *H. parahaemoliticus* are rare causes of endocarditis. *H. aegyptius,* the so-called Koch-Weeks bacillus, causes conjunctivitis while *H. ducreyi* is the cause of chancroid. *H. vaginalis* is a disputed cause of vaginitis. *H. aphrophilus* is rarely responsible for such infections as endocarditis, brain abscess, and pneumonia.[10] The pathogen responsible for pertussis is more properly referred to as *Bordetella pertussis.*

Organisms of the *Achromobacter* genus infrequently cause serious infections, such as bacteremia. The Mimeae tribe of organisms includes the species *Mima polymorpha, Herellea vaginicola,* and *Colloides anoxydana.*[11] These pleomorphic gram-negative rods are progressively attaining recognition as pathogens and may be confused with other bacteria, including *Neisseria* and *Haemophilus.* Infections said to be caused by Mimeae include conjunctivitis, vaginitis, urethritis, bacteremia, endocarditis, and meningitis. Infection due to *Vibrio fetus* resembles brucellosis in its pathogenesis and symptomatology and has been managed by a similar regimen. Whether the tetracyclines are useful in cholera is disputed; some workers believe replacement of fluid and electrolytes to be sufficient. This latter conclusion might tend to

TABLE 2

Gram-Negative Bacilli

- Enterobacteriaceae
  - Escherichia coli
  - Klebsiella-Aerobacter-Serratia group
  - Paracolobactrum or paracolon bacillus
    - Includes Arizona, Providence, Bethesda-Ballerup, and Hafnia groups

    } (coliform bacilli)
  - Proteus: P. mirabilis, P. vulgaris, P. rettgeri, P. morganii
  - Alcaligenes
  - Salmonella
  - Shigella
- Pseudomonas
- Bacteroides: B. fragilis, necrobacillus or B. funduliformis, fusospirochetes, Streptobacillus moniliformis
- Brucella: B. abortus, B. suis, B. melitensis
- Pasteurella: P. pestis, P. tularensis, P. multocida
- Haemophilus: H. influenzae, H. parainfluenzae, H. parahaemoliticus, H. aegyptius, H. ducreyi, H. vaginalis, H. aphrophilus
- Bordetella (Haemophilus) pertussis
- Achromobacter
- Mimeae: Mima polymorpha, Herellea vaginocola, Colloides anoxydana
- Vibrio: V. fetus, V. comma
- Actinobacillus mallei

Continued

corroborate the theory that symptoms of cholera may be due more to a toxin produced by the bacteria than to a more direct effect of the pathogen. *Actinobacillus mallei* causes glanders, and a sulfonamide is recommended.

Antibacterial Agents

In the management of infections due to gram-negative bacilli, the antibacterial agents listed in Table 3 have current or potential application. Data on the individual drugs will be presented in detail. It is obvious that drugs such as penicillin, erythromycin, and novobiocin which, as previously noted, may have use in the management of some infections due to gram-negative bacilli are not included, since their usual application is in infections due to other pathogens.

Streptomycin and Dihydrostreptomycin

Ototoxicity

Streptomycin is less likely to produce hearing loss than is dihydrostreptomycin or a combination of the two substances. Dihydrostreptomycin has produced deafness even after use of the drug has been stopped. It is recommended currently that dihyrostreptomycin be used only when the patient needs such an agent and can accept dihydrostreptomycin but not streptomycin. While streptomycin may damage vestibular function of the eighth cranial nerve, this is not so calamitous as deafness, and the dysequilibrium may be compensated, at least partly, by ocular mechanisms. Ototoxicity is best detected if audiometric and vestibular turning tests are done periodically during treatment and thereafter. The evidence of ototoxicity usually parallels the daily dose and duration of streptomycin therapy. The likelihood of ototoxicity is greater in infants, the aged, and those with impaired renal function. As a generalization, in normal adults, ototoxicity is unlikely if 2 gm. or less of streptomycin is given daily for no longer than 14 days, or 1 gm. is administered daily for four weeks or less. The blood concentration of streptomycin should not exceed 25 μg./ml., and the daily dose should be adjusted accordingly. A 0.25 to 0.5-gm. dose of streptomycin given every two to four days may suffice in the azotemic patient.

Concentrations of streptomycin in the perilymph may exceed those in the spinal fluid and may persist longer; also there may occur accumulation of the drug in the perilymph so that regular administration may further increase the concentration of streptomycin therein. Serum levels of the drug exceed concentrations in both the perilymph and spinal fluid. The relationship of the drug's concentration in the perilymph to the ototoxicity of streptomycin currently is conjectural.

In Pregnancy

With the exception of streptomycin, there is little exact evidence of fetal damage from administration of antibacterial agents to a pregnant woman, although other drugs appear to freely traverse the human placenta. There are reports of ototoxic residua in children born to mothers receiving streptomycin. Untoward effects of the tetracyclines, chloramphenicol, novobiocin, and the sulfonamides are such that one should appraise their use in pregnant women as perhaps being potentially hazardous to the fetus. The tetracyclines may form a calcium complex with the fetal skeleton and the de-

TABLE 3

Antibacterial Agents Having Current or Potential Use in Infections Due to Gram-negative Bacilli

Antibiotic Agents		Nonantibiotic Agents
Streptomycin	Polymyxin B.	The sulfonamides
Dihydrostreptomycin	Colistin	The nitrofurans
Neomycin	Cycloserine	Nalidixic acid
Kanamycin	Paromomycin	The methenamines
Gentamicin	Ampicillin	The acidifying agents
The tetracyclines	The cephalosporins	
Chloramphenicol	Spectinomycin	

veloping deciduous teeth; chloramphenicol may cause the fatal "gray syndrome" especially in premature infants, while novobiocin and the sulfonamides may adversely affect maternal and neonatal bilirubin metabolism. In premature infants this effect of the sulfonamides may increase their susceptibility to kernicterus.

It is not definitely known if prior use of streptomycin or other ototoxic drugs like kanamycin increases the chance of ototoxicity on future use of streptomycin, but this possibility should be considered when the drug is administered. In any event, ototoxic drugs should not be used concurrently.

Curariform Action

Streptomycin,[12] dihydrostreptomycin, neomycin, kanamycin, polymyxin B, and colistin share a potential curariform action which may produce neuromuscular block and respiratory arrest,[13] especially on intracavitary instillation. Such an effect would be unusual when streptomycin is given intramuscularly; but the possibility is considered in infants, the aged, patients with renal disease or hypoxic states, and those receiving drugs such as muscle relaxants, sedatives, narcotics, and anesthetic agents. In patients having such an untoward reaction, use of neostigmine or calcium may be helpful. The previously mentioned antibiotics are contraindicated in patients who may have myasthenia gravis.

Other Undesireable Reactions

Optic neuritis may follow the administration of either streptomycin or chloramphenicol and is a theoretic reason for avoiding concurrent use of these drugs.

Fever, rashes, paresthesia, headache, and rarely pericarditis may result from the use of streptomycin.

Indications

Currently, streptomycin is used mainly in combined therapy, as with penicillin in management of enterococcal endocarditis and with a tetracycline in treatment of such conditions as brucellosis or pneumonia due to *K. pneumoniae*. Incidentally, the antienterococcal effect of combined streptomycin-penicillin therapy may be the best clinical example of an enhanced antibacterial effect. Use of streptomycin against tuberculosis along with other agents hardly requires reiteration. Tularemia is one of the few diseases in which streptomycin currently is employed alone with good results.

Neomycin

Intramuscular use of neomycin (Mycifradin) has decreased, especially since the advent of kanamycin. Neomycin, like kanamycin, has limited anticoccal action, and generally this is chiefly antistaphylococcal; in addition it is effective against strains of Enterobacteriaceae. Bacterial resistance to neomycin has increased in recent years, perhaps because neomycin is incorporated in procedures used to prepare the colon before the operation, and also because the drug is a constituent of numerous preparations for local use, such as sprays and creams. In this regard, neomycin, kanamycin, and paromomycin may be cross-resistant, and there is partial bacterial cross-resistance among these drugs and streptomycin.

Indications

Because of its potential nephrotoxicity and neurotoxicity when administered systemically, neomycin is reserved principally for (1) topical application, (2) preoperative preparation of the colon, and (3) certain cases of hepatic coma. It has also been given orally, both alone and with polymyxin B in cases of enteric salmonellosis and shigellosis.

Contraindications

Since neomycin is not absorbed well from the intestine, as much as 8 to 12 gm. has been given daily by the oral route in certain patients, such as those with hepatic coma. Preferably, no more than 4 gm. orally per day should be given, especially in patients with hepatic or renal disease, because blood concentrations may become so high as to induce toxic effects. If neomycin is given intramuscularly, a daily dose of 1 gm. should not be exceeded.

Neomycin-induced *ototoxicity* principally

Continued

involves auditory function and is irreversible. It has occurred after the drug has been used orally, intramuscularly, as an aerosol, and after topical application to cutaneous burns.

In addition to neomycin, there are five drugs that can cause *paresthesias*, usually circumoral and of the acral parts; these same drugs are capable of a curariform effect and are streptomycin, dihydrostreptomycin, kanamycin, polymyxin B, and colistin.

Malabsorptive Effects

Malabsorptive effects on oral use of neomycin may resemble those of nontropical sprue and include steatorrhea, azotorrhea, and interference with the absorption of vitamins, sugars, and minerals, as well as small-bowel alterations on biopsy. Neomycin-induced malabsorption may be the basis for the hypocholesterelemic effect that occurs after the drug is used orally.

Contact dermatitis from local use of neomycin occurs.

Neomycin, streptomycin, the tetracyclines, and other drugs may depress the gram-negative elements of the normal flora and allow overgrowth of resistant staphylococci. Bacteremia, pneumonia, and other staphylococcal superinfections may occur in addition to staphylococcal enterocolitis.

Kanamycin

The antibacterial spectrum of kanamycin (Kantrex) closely resembles that of neomycin. Kanamycin has use against staphylococci and strains of *E. coli*, *Klebsiella-Aerobacter*, *Proteus*, *Salmonella*, and *Shigella*, but it is not active against all *Pseudomonas* organisms and usually is ineffective against streptococci, pneumococci, and *Bacteroides* organisms. Organisms show almost complete cross-resistance to neomycin, paromomycin and kanamycin as well as one-way cross-resistance to streptomycin and kanamycin or the other drugs; that is, organisms resistant to kanamycin are resistant to streptomycin, but organisms resistant to streptomycin may be sensitive to kanamycin.

The daily intramuscular dose for an adult of average weight is 1.0 gm. and should not exceed 1.5 gm., even for heavier patients. Rarely is kanamycin given intravenously.

Injection of kanamycin directly into the gallbladder during laparoscopy in the management of typhoid carriers has been recommended when less heroic measures have failed.

Ototoxic Effects

One should be hesitant to continue therapy beyond 10 days because of the drug's capacity to cause deafness which may be delayed in onset and is irreversible. Other untoward effects include rashes, fever, nephrotoxicity, curariform action, paresthesia, and superinfection.

In addition to kanamycin, there are at least five other potentially ototoxic drugs: streptomycin, dihydrostreptomycin, neomycin, gentamicin[13] and vancomycin. Whether ristocetin or colistin is ototoxic is uncertain. One should avoid concurrent and perhaps sequential use of these ototoxic drugs.

Gentamicin

Gentamicin (Garamycin) is available only for investigational use. The antibacterial spectrum and toxicity of gentamicin resemble those of neomycin and kanamycin, but gentamicin may be more effective against *Pseudomonas* organisms. Gentamicin is poorly absorbed from the gastrointestinal tract and for systemic effect is given intramuscularly. Adults have received a total daily dose of 50 to 100 mg., given in two or three intramuscular injections for as long as 10 days. However, the drug has been used successfully by the oral route in enteric infections and on intramuscular injection in urinary infections.

Vestibular damage, which may be of delayed onset is the chief hazard of gentamicin therapy. Of the ototoxic drugs, streptomycin and gentamicin are more likely to cause vestibular damage, whereas dihydrostreptomycin, neomycin, kanamycin, and vancomycin are more likely to induce deafness.

Other untoward effects include nephrotoxicity, increased serum glutamic oxaloacetic transaminase activity, superinfection, fever, and rashes.

References may be secured from the author or reprints.

Abstracts, Briefs and Commentaries

INTRADUCTAL PAPILLOMA OF THE BREAST

"A discharge from the nipple must always, except during pregnancy or lactation, be considered a sign of a disease in the underlying mammary tissue, regardless of whether the discharge is serous, serosanguineous, or hemorrhagic*." The most common cause is an intraductal papilloma, but as a rule it co-exists with other changes of glandular tissue. When a mass or lump is also palpable, the percentage of carcinoma increases.

Judd reported 100 patients with this sign, 57 per cent of whom had cancer. All patients with cancer had a palpable lump. Bloodgood found that of patients with a nipple discharge without a palpable lump, only one per cent had cancer. Among 108 patients with bleeding nipple, Adair found malignancy in 47 per cent and, supported by Cheatle and Cuttler and by Kaal, expressed the opinion that papillomas might become adenocarcinomas. In a series of 87 patients with bleeding nipple and a malignant tumor, Gray and Wood found 60 per cent to have no palpable changes. They make a distinction between two types of papillomatous tumors of the breast, viz., benign intraductal papilloma, fairly common, and malignant, papillomatous carcinoma. The validity of their histological diagnoses has been questioned by Haagensen et al. Saltztein and Pollock found no malignant tumors among a series of patients with bleeding nipple only, while several others reported from two to twelve per cent.

There are different views expressed on the type of treatment. Local excision with meticulous care is described by Haagensen with but two recurrences in five years of follow-up. However, a simpler method advocated by Babcock, who advises the excision of a wedge of the breast including the whole duct, is not only technically easy but gives a good cosmetic result.

The authors report 80 Babcock resections on 77 patients. All had nipple discharge and 14 a palpable tumor. Sixty per cent had their operation within six months of onset of bleeding and 70 per cent within the first year. Thirty-five patients underwent surgery before their menopause and 36 after. The majority of these patients were between 40 and 55 years of age, while the preponderance of malignant tumors occurred in women between 60 and 65 years of age.

Mammography was done on 69 operated patients prior to surgery, with

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2.8 per cent considered failures: a far cry from the statistics of the Houston group. In 44 cases, however, mammography gave a suspicion of intraductal disease.

Among 14 patients with a palpable mass, four had cancer; of the entire group, 10 had cancer. Their follow-up is inadequate for conclusions in view of the small number of patients, the brevity of time, and the number who have not returned for examination.

The authors conclude definitely that all patients with discharge from the nipple, serous or hemorrhagic, should be subjected to surgical treatment because of the possibility of malignancy.

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Andersen, A., and Koudal, G.: Department of Surgery, Finseninstitutet and Radiumstationen-Copenhagen, Denmark. Acta Chir Scand Supplementum 343, Stockholm 1965.

ANASTOMOSIS BY GLUING

Several drops of surgical adhesive (Eastman 910 Monomer) were placed between the overlapping bowel edges in doing experimental anastomosis on a dog's intestines. These studies were conducted on both the large and small gut, and a comparable series of controls by standard suture methods were used.

After removing about one inch of mucous membrane from the distal loop, the proximal loop was pulled into the denuded area with sutures. The tissues were then glued together and the sutures removed.

Though the authors do not suggest that the method is yet clinically applicable, they believe that it offers enough potential to warrant further investigation. In their dog experiments they obtained good results in a very high percentage of the cases.

Editor's Note: This is a new procedure which deserves watching.

Carl O. Rice, M.D.
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Lynn, Bernard S., Cecil, Fred, Conly, Patrick, Canaday, Wm. R., and Wolcott, Mark W.: Intestinal Anastomosis by Invagination and Gluing. Amer J Surg 111:197, 1966.

CIRRHOSIS AND VARICES

A group organized to study diseases of the liver followed 471 patients with cirrhosis and esophageal varices at 7 co-operating hospitals. Only 8% of the 471 had had prior hepatitis while 83% of these patients were alcoholic, 96% had jaundice, ascites, or hepatic pre-coma singly or in combination, and 51% had massive upper gastrointestinal bleeding. The major causes of death were hemorrhage in 34%, hepatic failure in 32%, renal shutdown in 11% and infection in 9%. Despite vigorous treatment, survival 1 year after demonstration of varices was only 34%, and the survival curve for this group almost duplicates the curves obtained by Ratnoff and Patek in their analysis of patients with decompensated cirrhosis who entered 5 New York hospitals in the years 1938-1961. Reasons are suggested for the failure of improvement in survival despite the acknowledged advances in the understanding and treatment of cirrhosis and its complications.

Courtesy of References and Reviews
Journal of the American Medical Association

Garceau, A., and Chalmers, T.: New Engl J Med 268:469, 1963.

NEUROTICISM AND HYPERTENSION

This report examines the hypothesis that hypertension is a psychosomatic illness. Neuroticism, defined as emotional over-responsiveness and a tendency to break down under stress, and extroversion, defined as a tendency to be outgoing and sociable, were measured on the Maudsley Personality Inventory (MPI), which was given to four groups of patients. The first group, 459 patients, had psychosomatic disorders; the second group, 231 patients, had possible psychosomatic disorders; the third group, 116 patients, had neurotic disorders; and the fourth group, 546 patients, were normal controls.

The following psychosomatic disorders were associated with a significantly elevated neuroticism score: dysmenorrhea, urticaria, leukorrhea, fungus infections, alopecia, asthma, eczema, menorrhagia, irregular menstruation, seborrhea, dermatitis, psoriasis, hypertension, diabetes, dermatosis, chronic nasal infections, thyrotoxicosis, and rheumatoid arthritis. Psychosomatic conditions not associated with significantly elevated neuroticism scores included peptic ulcer, pruritus, acne vulgaris, and coronary artery disease. In the 19 hypertensive patients the mean level of neuroticism was significantly higher than in the normal controls and it was also significantly higher than in the 67 patients who had chronic organic disabilities resulting from poliomyelitis, cancer, and congenital abnormalities. The extroversion scores of the hypertensive patients were significantly lower than those of the controls. Patients diagnosed as neurotic naturally had higher neuroticism scores than did patients diagnosed as having psychosomatic conditions, and, conversely, patients with illnesses considered to be possibly psychosomatic in origin (cervical erosion, herniated discs, obesity, sterility, etc.) had lower neuroticism scores than patients in the psychosomatic-illness group. Interestingly, patients with heart ailments other than hypertension (including rheumatic valvular heart disease and coronary artery disease) did not have elevated neuroticism scores. These findings suggest that emotional illness did not result from hypertension but that it was a possible causal element in the development of hypertension. From this investigation it appears that patients with psychosomatic illnesses, and especially with hypertension, are intrinsically more neurotic, more emotionally labile, and have a greater propensity to break down under stress than people without hypertension.

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Sainsbury, P.: Neuroticism and Hypertension in an Outpatient Population. J Psychosom Res 8:235, 1964.

MISSED APPENDICITIS: A CONTINUING DIAGNOSTIC CHALLENGE

In spite of advances in diagnosis, recognition of appendicitis often becomes a major problem. An estimated 200,000 cases are recognized in the United States each year associated with an over-all mortality of one per cent. Perforation with abscess and peritonitis is the most important factor. The authors report about one in six to have this complication, which definitely increases the mortality when accompanied by co-existing disease and when encountered in the very young, the very old, and pregnant women. Effort to prevent perforation of the appendix means early diagnosis and oper-

Continued

ation within 36 to 48 hours. The authors review the classical symptoms of epigastric pain, nausea or vomiting, local tenderness, fever, and leukocytosis. Features suggesting appendiceal rupture are: duration of symptoms longer than 48 hours, elevation of temperature to 103°+, physical signs of peritonitis, and a leukocyte count of 20,000. General peritonitis after rupture of the appendix is not inevitable. However, a pelvic abscess without other characteristic features due to perforation of a pelvic-lying appendix is easily overlooked and therefore one of the most dangerous conditions in the abdomen. The mortality rate is about 12 per cent in spite of modern methods of treatment.

A very extensive report of missed appendicitis in a student follows: He had fatigue, malaise, chills, and a temperature of 105°. He also had symptoms of upper respiratory infection and vomiting, for which he was treated by his local physician, with improvement on antibiotics. Later he developed lower abdominal pain, fever, and diarrhea; and during about three weeks he lost 21 pounds in weight. At this time he was admitted to a hospital under the care of the Cleveland Clinic. Complete examination revealed no rebound tenderness and no pelvic mass. Laboratory examinations were negative; however, x-ray studies revealed a large pelvic abscess. He improved on management with tetracycline, 250 mgm. four times daily for two weeks, and was discharged.

The diagnostic dilemma of a long-standing appendiceal abscess (missed appendicitis) may be difficult to resolve, but the therapeutic dilemma may be even more of a problem.

Crile states that an appendiceal abscess can be treated conservatively with antibiotics. Other surgeons have agreed that after an abscess has developed, treatment with antibiotics is as successful as surgery. If the symptoms of an appendiceal abscess are recognized early, most investigators continue to recommend operation. The importance of early diagnosis of appendicitis and appendectomy is emphasized.

Comment

The operative mortality quoted here seems unduly high unless all complicated or missed diagnoses are included. Drainage of a pelvic appendiceal abscess via an abdominal incision has a definite hazard. The drainage via the rectum of an abscess in direct contact with it seems to have been forgotten. Before antibiotics we found it to be a very safe procedure. Evidently the review of the early symptoms of acute appendicitis may be timely.

Stanley R. Maxeiner, Sr., M.D.
Minneapolis, Minnesota

Farmer, Richard G., and Turnbull, Rupert B., Jr.: Cleveland Clin Quart, July 1965.

Ptolemy VII

Ptolemy VII was one of the fattest men of antiquity who was so obese that he could not walk unless supported from both sides. Another tiny tot of antiquity was Denys of Heraclea, who was so fat that he hardly dared to go to sleep for fear of suffocation. To keep him awake it was necessary to place needles in the back of his chair so that he would immediately be awakened as soon as he became relaxed.

— F. William Saul, M.D.: Pink Pills for Pale People

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In Donnatal, natural belladonna alkaloids are rationally balanced in a specific, fixed ratio that provides "the greatest efficacy with the smallest possible dose."[1] They avoid the clinical uncertainties of the variable tincture and extract of belladonna, and are considered superior in range of action to atropine alone.[2] Furthermore, they are generally recognized as being more effective than the synthetics for relieving visceral spasm.

phenobarbital for sedation

Years of clinical use have established phenobarbital as one of the most efficient and highly regarded sedatives. In fact, for general sedation it is the drug of choice.[3] In Donnatal, phenobarbital potentiates the spasmolytic effects of the belladonna alkaloids, lessening emotional tensions and checking the neurogenic impulses that trigger GI disorders.

more than 24 indications in PDR

Donnatal has withstood the test of time to become the classic sedative-antispasmodic because of its unsurpassed effectiveness, safety, economy, uniformity of composition, and dosage convenience. Its widespread acceptance and usage by the profession can also be attributed to its versatility in treating disorders characterized by smooth muscle spasm. There are more than two dozen distinct and separate indications for Donnatal listed in the current PDR.

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hyoscyamine sulfate	0.1037 mg.
atropine sulfate	0.0194 mg.
hyoscine hydrobromide . . .	0.0065 mg.
phenobarbital	(1/4 gr.) 16.2 mg.

(warning: may be habit forming)

IN EACH EXTENTAB

hyoscyamine sulfate	0.3111 mg.
atropine sulfate	0.0582 mg.
hyoscine hydrobromide . . .	0.0195 mg.
phenobarbital	(3/4 gr.) 48.6 mg.

(warning: may be habit forming)

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REFERENCES: 1. Vollmer, H.: Arch. Neurol. and Psychiat., 43:1057, 1940. 2. Morrissey, J.H.: J. Urology, 57:635, 1947. 3. Krantz, J.C., Jr., and Carr, C.J.: Pharmacological Principles of Medical Practice, 2nd ed., Baltimore (1954), 552.

*This one at Westover, elegant Colonial Virginia plantation, located on the James River near Richmond. Built in the early 1730's by William Byrd II, founder of Richmond, it is now the home of Mrs. Bruce Crane Fisher.

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1. Schleif, R.H.: J.A.PH.A., 46:179,1957 *U.S. Pat. No. 3,062,714

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Book Reviews

"There can be nothing so gratifying to an author as to arouse the respect and esteem of the reader. Make him laugh and he will think you a trivial fellow, but bore him in the right way and your reputation is assured." — William Lyon Phelps

NEURO-OPHTHALMOLOGY — **(Vol. II) Symposium of the University of Miami, Edited by J. L. Smith, M.D., C. V. Mosby Company, St. Louis, 278 pages, chapter references, index, illustrated — price $21.75.**

This book covers in detail selected topics of current interest to the contributors. Thus, rather than being a comprehensive text, it serves as an excellent source of information and references on the topics presented and would be of use to several specialties.

Chapter 1 by J. L. Smith, M.D., emphasizes the importance of the pupillary reactions and T.P.I. test in detecting seronegative syphilis. In Chapter 3, D. G. Cogan, M.D., has divided heredodegenerations of the retina into four anatomic categories based on the cell areas involved until they can be classified biochemically. This has been possible so far in only several of the many syndromes. E. W. D. Norton, M.D., presents his interesting work on fluorescein angiophotography of the fundus. This has shed light on the differential diagnosis of fundus lesions which are mistaken for malignant melanoma as well as on diabetic retinopathy. The test is clinically applicable using a modified Zeiss fundus camera. Chapter 10 provides a complete monograph on the anatomy, physiology, and clinical aspects of the seventh cranial nerve and the articularis oculi by W. F. Hoyt, M.D. The reader appreciates that eyelid tics are not always benign. N. J. David, M.D., reviews the syndromes of the basilar artery and emphasizes the importance of Horner's syndrome in softenings of the lateral medullary plate. The volume concludes with a well illustrated discussion of the so-called phakomatoses, including Bohrneville's, Von Recklinghausen's, Sturge-Weber and Von Hippel-Lindau syndromes.

William S. McClanahan, M.D.
Minneapolis, Minnesota

APPLIED VIROLOGY — **Murray Sanders and Edwin Lennette (Editors), Olympic Press, Sheboygan, Wisc., 1965, $7.50, 319 pages.**

This paperback volume contains the proceedings of the First Annual Symposium on Applied Virology. Seventeen papers, given by 30 virologists from four countries, cover subjects ranging from diagnostic techniques to viral zoonoses to oncogenesis by viruses. The editors trim the talks and discussions to readable form and retain some excellent illustrative material. Included are such practical and current topics as collection of specimens, interpretation of results, use of flourescent-antibody techniques, role of *Mycoplasma* organisms in human disease, experiences with live vaccines in upper respiratory infections, and advent of antiviral agents. The book will be rewarding for physicians interested in viral disease.

Richard L. Reece, M.D.
Minneapolis, Minnesota

COMMUNICABLE AND INFECTIOUS DISEASES — **Franklin H. Top, 5th edition 1964. C. V. Mosby Company, 920 pages.**

This is the 5th edition of an established reference monograph on communicable and infectious diseases; twenty-five outstanding authorities on infectious diseases have contributed to this edition. The book is primarily intended for the clinician. The first section is devoted to general consideration of epidemiology, regulation and control of communicable diseases, chemotherapeutic and antibiotic agents and their reaction. Included in this general section are two excellent chapters on the management of communicable diseases in the hospital and the home. The remainder of the book is devoted to a discussion of primarily the clinical considerations in diagnosis, course and treatment of viral, fungus and infectious diseases, which are classified according to their portal of entry into the body and the main organs involved with the infectious agent. This creates some problems in using the book as a quick reference for specific infectious diseases; however, it has the advantage of discussing the various diseases in relation to their primary clinical manifestation.

The text is very well illustrated with both black and white and color illustrations and has quite complete references at the end of each section. I found the book to be comprehensive and detailed in its discussion, yet relatively easy to read and use as a reference text. This book will be a very useful and interesting one to all physicians encountering communicable and infectious diseases in their patients.

Alvin L. Schultz, M.D.
Minneapolis, Minnesota

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Gleanings from the Meetings

Annual Meeting
Society of Thoracic Surgeons
Denver, Colo. Jan. 24-26, 1966

Mediastinotomy

Diagnostic anterior mediastinotomy is a relatively simple procedure as described by Drs. McNeill and Chamberlain.* The procedure is diagnostic, employed only in patients with thoracic disease beyond surgical intervention.

The procedure is an extrapleural approach via the bed of the second costal cartilage. If desired, the pleura can be opened and a lung biopsy obtained. General anesthesia is employed. Scalene node removal is done first.

This approach has the advantage of a more thorough exploration of the mediastinum than can be obtained by midline mediastinoscopy. The disability is no greater and the yield of positive results higher. Likewise, control of bleeding, etc. would seem easier.

Mediastinitis

Progressing fibrosing mediastinitis and histoplasmosis may have a direct relationship. Drs. Hewlett, Steer, and Thomas** presented evidence of this relationship in 14 patients, 12 of whom had the progressive debilitating form of disease.

Not all patients with enlarged mediastinal nodes of histoplasmosis infection will develop the progressive pseudotumor invasion of the mediastinum. However, if the disease does "break out" of node encapsulation, no known medical or surgical treatment will prevent progressive venacaval obstruction, bronchial stenosis, and death from invasion by the sclerosing process.

The authors suggest early surgical removal of noninvasive enlarged lymph nodes secondary to histoplasmosis. The photographs of autopsy specimens of the final stages support this attitude.

Editors note: Minnesota is an endemic area of histoplasmosis. Physicians should be alert to this disease and perform skin tests and serum agglutinin titers on all patients with mediastinal node enlargement.

Permanent Pacemaker Insertion — An Appraisal
— V. Parsonnet, M.D., L. Gilbert, M.D., I. R. Zucker, M.D.

The authors related their experience with 87 patients who had an electrical pacemaker for atrioventricular block. One hundred and three pacemaker units were placed by either intravenous, transthoracic, or transdiaphragmatic route. There was one operative death. Thirty patients required more than one operation before a satisfactory function pacemaker unit was achieved; failures were related to the apparatus and technique of placement.

The safest technique for bad-risk patients is the transvenous via the left cephalic vein, permanently implanting the battery in the subpectoral area

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*"Diagnostic Anterior Mediastinotomy." T. M. McNeill, M.D., J. M. Chamberlain, M.D.

*"Progressive Fibrosing Mediastinitis." T. H. Lewlett, M.D., A. Steer, M.D., D. E. Thomas, M.D.

Continued

under local anesthesia. Two years' experience suggests this may be the route of choice. No anticoagulants are needed.

One discussant (J. H. Kennedy) suggested performing cardiac output determinations before and after pacing with the transvenous electrode. If the cardiac output falls with electrical pacing, primary myocardial insufficiency contraindicates further pacing.

The other techniques of operative insertion were described. However, the transvenous approach seems most logical if the reported low morbidity remains valid with further passage of time.

Evaluation of a Technique to Prevent Aortic Regurgitation Using the Magovern Prosthesis — N. Zuhdi, M.D., J. Carey, M.D., A. Greer, M.D.

An interesting solution was presented to offset the problem of postoperative regurgitation about the Magovern sutureless aortic valve prosthesis. This prosthesis has the advantage of quick, easy multiprong fixation after removal of a diseased aortic valve. However, despite modifications of the prosthesis, most surgeons find a major number of patients with audible aortic regurgitation — i.e., the valve rim does not effectively seal against the aortic wall. The degree of regurgitation may become hemodynamically significant and therefore a serious postoperative complication. Various techniques to prevent this have been devised.

Dr. Zuhdi has approached this problem utilizing principles of resultant forces in/during the thrust of volume expansion of a tube (the aorta) with a fixed point (the aortic valve annulus). The resultant lateral vector force is at this point — the apex of the angle of aortic expansion — and the site of regurgitation; therefore Dr. Zuhdi minimizes this lateral vector by preventing aortic expansion and narrowing the angle thereof. He wraps the ascending aorta with a one-inch teflon cloth and thereby prevents regurgitation.

An interesting application of mechanics.

Gulliver's Travels — Jonathan Swift*

Gulliver — On Crooked Politicians

"The Palace of a chief minister is a seminary to breed up others in his own trade: the pages, lackeys and porters by imitating their master, become ministers of state in their several districts and learn to excel in the three principal ingredients of isolence, lying, and bribery. Accordingly, they have a subaltern court paid to them by persons of the best rank; and sometimes by the force of dexterity and impudence, arrive through several gradations to be successors of their lord.

He is usually governed by a decayed wench, or favored footman, who are the tunnels through which all graces are conveyed, and may properly be called, in the last resort, the governors of the kingdom.

By 'an act of indemnity' they secure themselves from after-reckonings, and retire from the public, laden with the spoils of the nation."

— Heritage Press, 1940

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*See Minnesota Med 49:692, 1966 for second installment.

(To be continued)

Special Article

Normal Values

PAUL J. ALEXANDER, M.D.*
Minneapolis, Minnesota

". . . and the serum sodium is 134 mEq/L."

THE CLINICIAN is called upon daily to assess measurement values ranging from serum sodium concentrations to blood pressure readings. Decisions about the meaning of such measurements are based on his evaluation of multiple variables including a comparison with the results that might be expected if the patient were *not ill.* In other words, each step of the diagnostic process calls for a comparison between the patient's values and *Normal Values.*

In the hypothetical report cited above one must decide whether this value is normal, i.e., within the range of physiologic variation, or whether it is abnormal. Will the patient need further investigation or specific therapy? Obviously, the physician would want to gather more information about his patient before arriving at a conclusion. One thing he would want to know would be the normal value of serum sodium. He would consult the pathologist concerning his laboratory's experience, and since the individual laboratory generally establishes normal value limits on a small number of subjects, the clinician and the pathologist must together consider the values reported in the standard textbooks, as shown in Table 1.

If uncertain after consulting the textbooks and finding no indication of the populations on which the information was based, they might consult original articles dealing, for example, with normal values of serum or plasma sodium as measured by flame photometry, as shown in Table 2. If the patient did not happen to be a "normal adult," the issue would depend on clinical information and other laboratory data. The doctor's dilemma serves as an example of the unquestioned importance of meaningful standards for evaluation of laboratory data.

Just how *normal* are normal values?

This discussion will be limited to the general field of laboratory medicine, although the principles apply equally well to the parent discipline of biometry. The inclusion of this article in a special edition dedicated to Dr. Gerald T. Evans is appropriate for several reasons. Most important is the fact that normal values must be based on good measuring devices, e.g., a reliable laboratory. It is for this that Dr. Evans has devoted 25 years of service to the University of Minne-

Continued

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*Assistant Professor, Department of Laboratory Medicine, University of Minnesota.

sota. He has always emphasized the importance and difficulty of establishing good, normal values based on the highest quality of practical measurement. The growth of laboratory medicine reflects the burgeoning knowledge in the basic sciences. These are being translated into clinical applications by the combined efforts of well-informed clinicians and the efforts of men like Dr. Evans who have chosen to build a bridge between the basic and applied sciences. One of the recognized foundations of such a bridge is the concept of normal values, the subject of this article.

Semantics

Terminology is a problem that needs consideration. Albritton[9] and others have used the term "standard"* values, but the term "normal"** is the more commonly used and according to its definition,[10] it is more appropriate. Sunderman[11] refers to the "norm" as a selected range of values obtained from apparently healthy people whose individual values would then be classed as "normal." Consideration has even been given to establishing "ideal" values rather than the "normal" values based on averages, but too little information exists on what is really "ideal." In this paper the term "normal values" will be used.

Variability

Table 3 lists some of the factors which affect medical laboratory measurement. Because of increased use of quality control techniques the clinician expects to know from the laboratory what the "confidence limits" are for a particular test. For example, with serum sodium he might expect the value reported as 134 mEq/L to actually lie somewhere between 131 and 137 mEq/L in 95% of replicate determinations of the same specimen.[12]

Different methods and laboratory variation also affect tables of normal values. The measurement of sodium by flame photometry is a reliable method; yet methodology[13] may be one of the factors contributing to the apparent inconsistencies appearing in Tables 1 and 2. Methodology in other tests, e.g., red blood count and uric acid, plays a more important role in affecting differences between results from various laboratories.

TABLE I
Normal Values of Serum as Recorded in Various Textbooks

Range meq/L	Senior Author or Editor	Title	Year
130-143	Gradwohl, R. B. H.	Clinical laboratory diagnosis	1963
130-143	Levinson, S. A.	Clinical laboratory diagnosis	1961
132-142	Harrison, T. R.	Principles of internal medicine	1962
133-143	Eastham, R. D.	Biochemical values in clinical medicine	1960
133-148	Davidsohn, I.	Todd & Sanford's clinical diagnosis by laboratory methods	1962
136-145	Beeson, P. B.	Cecil-Loeb's textbook of medicine	1963
136-145	Goodale, R. H.	Clinical interpretation of laboratory tests	1964
136-145	Page, L. B.	A syllabus of laboratory examinations in clinical medicine	1960
136-145	Roberts, H. J.	Difficult diagnosis, a guide to the interpretation of obscure illness	1958
136-148	Wilkinson, R. H.	Chemical micro-chemical methods in clinical medicine	1960
138-145	Miller, S. E.	A textbook of clinical pathology	1960
138-148	Hoffman, W. S.	Biochemistry of clinical medicine	1964

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*The pertinent sections read: *Standard:* ". . . 3. Something that is established by authority, custom or general consent as a model or example to be followed. 4. Something that is set up and established by authority as a rule for the measure of quantity, weight, extent, value or quality."

***Normal:* ". . . 3.b. Occurring naturally and not because of diseases, inoculation or any experimental therapy. 4.c. Characterized by balanced and well integrated functioning of the organism as a whole within the limits imposed by the environment and in accord with the pattern of one's biological endowment. 6. Approximately the statistical norm or average.

In attempting to arrive at limits which apply to a population, both method variations and variations in the same person contribute to the range and, additionally, there is the unique factor of the difference *between* individuals. This last item can be illustrated by using the height of an adult. The height of a single individual would vary only slightly if measured day to day. The range of normal values for height in a population leads to a wide range of *inter-individual* variability due to factors cited in Table 3. Inter-individual variations are assumed not to be as great for most laboratory tests.

The example of serum sodium not only illustrates the inconsistency of reported normal values, but makes obvious the problems of the borderline value. Had the value been reported as either 127 or 140 mEq/L, the implications would be much clearer. But the area where the normal population values overlap the abnormal ones is where

TABLE 3
Variables in Medical Laboratory Measurements

Patient Factors
- Condition
  - Physiologic: e.g., fasting, post exercise, pregnant.
  - Pathologic: This is generally the variable which is under consideration for determination.
- Age
- Sex
- Environmental: e.g., altitude, urban or rural, climate, socioeconomic.
- Genetic: Race, familial disposition.
- Time of specimen collection: Period of collection, diurnal variation, cyclic phenomenon.

Methodology
- Collection technique
- Preservation of specimen
- Measurement technique: Precision and accuracy.

TABLE 2
Normal Values of Serum (or Plasma) Sodium Measured by Flame Photometry as Recorded in Original Investigations

Range meq/L	Average	Standard Deviation	Year	Number of Subjects	Senior Author and Comment*
132-144	--	--	1963	157	Flear, G. T. G.:[1] 85 females and 72 males between the ages of 16 and 55. Hospital employees.
133-152	--	--	1953	50-100	Wooton, I. D. P.:[2] Aged 18-50; fasted four hours; no known systemic disease.
135-145.5	139.8	3.8	1962	13	Salminen, S.:[3] 6 males and 7 females in good general condition. Hospitalized for such reason as slight mental disorders.
135-155	144.7	3.81	1951	400	Elliot, H. C.:[4] Fasting blood bank volunteers evenly distributed as to sex and age. Histogram compatible with normal distribution and some left-tailing.
135.5-153.2	144	3.6	1947	107	Marinis, T. P.:[5] Normal blood bank donors.
136-158	142	--	1950	70	Smith, R. C.:[6] Normal, young adult fasting subjects.
139-151	144	--	1950	20	Wynn, V.:[7] Normal subjects.
140-159	153	--	1947	60	Overman, R. R.:[8] Human subjects.

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*In general, the commentary includes *all* of the information described in the original articles with regard to the age and sex distribution and the health status of the sample.

Continued

the physician needs the greatest help from meaningful measurements in healthy people with as many of the same variable factors as in his own patient. Unfortunately, the dilemma posed by Tables 1 and 2 is often worse for other parameters which do not share the relatively narrow range of serum sodium or the relative precision of measurement of this element by flame photometry. There is need in normal value tables for a definition of the characteristics of the population from which the "yardsticks" are derived.

Normal Value Data Sources

In 1949 Sunderman and Boerner,[11] in a remarkable publication, compiled tables with specific reference to studies of normal values. Unfortunately, their activity seems to have aroused little interest or enthusiasm. We still know little about the "normal" range of the "normal" population.

Small Healthy Group

The "ten-handiest-people" approach is well established and convenient but has little else to recommend it. Usually there is a marked bias in age and sex selection, making any extrapolations unreliable. Generally the health of subjects is assumed rather than proved, but the smallness of the group makes control of the health factors easier than with larger groups.

Larger Selected Groups

In these studies, medical students and student nurses are often used; but also armed forces, inmates of penal institutions, blood bank donors, well-baby clinics, and other special aggregations are employed for determinations. Such groups are large and in good health and can provide fairly good data. The age-sex selection bias in such groups may be an advantage in applying the values to similar individuals, or, in statistical terms, the cohort group. The extrapolation of data to more heterogeneous populations should be done only after making sure that the original group is a valid sample of the larger population.

Routine Laboratory Data

Recently Hoffman[14] has emphasized the potential of utilizing routine hospital or office laboratory data to determine normal values. This proposal is of particular interest because, if its reliability were to be established, the values obtained would be much more closely based on the local situation than the usual standard tables. However, this technique demands certain important assumptions which need to be tested in practice. The system is based on the premise that a great majority of specimens routinely analyzed in the laboratory show results which fall close to the previously suggested normal values. Hoffman has manipulated this data by statistical means and with some arbitrary exclusions has divided these into normal and abnormal groups and has used the former as the basis for the normal values for a particular laboratory.

Epidemiologic Approach

In contrast to the sample bias inherent in the previous categories, an effort to select random samples from the healthy population at large would most nearly ascertain the *truly* normal value range of any given characteristic. Such an undertaking is expensive, time-consuming, and difficult to achieve. It has been done in surveys of limited population groups and in a modified form recently for a single community,[15] but it includes in its shortcomings the problem of the definition of normality. The possibility that a representation of abnormals might be included by design would actually help to clarify the critical area of overlap between high (or low) normal subject values and low (or high) abnormal subject values. However, that would entail even greater work in defining the health status of the population studied.

Individual Normal Values

Previously, in defining normal values, it has been assumed that because of the inherent variation between individuals, the determined range for a group in respect to any one variable would exceed the range of any normal individual responding to the usual physiologic stresses. Accordingly, it can be postulated that in some instances an individual may become ill and several of his values change significantly from his normal range and yet still lie within the broader range of the group normal values. Schneider[16] discusses and illustrates this point as regards transaminase determinations.

In essence, this is an extension of the principle already applied in establishing a "base line" EKG or an initial chest x-ray. It is hoped that eventually it will be possible to determine by periodic reexamination a range of values that will meaningfully define each patient's individual variation in health.

If such a program were to be widely adopted, it would require a great increase in the volume of prophylactic or data-gathering determinations from asymptomatic patients. Increased emphasis on laboratory stability (defined variability over long periods of time) and interchangeability of data from laboratory to laboratory would be desirable. It would still be necessary, however, to have inter-individual data values, but these could be obtained from information available in multiple individual patients' profiles.

In general, data obtained from any special group has limitations in its applicability. These limitations are best understood when the group is well defined and its relationship to the individual patient is clear. This principle emphasizes the importance of categorization of normals where meaningful differences can be established. For example, although there is evidence to the contrary[17] it is generally assumed that the value of serum sodium is not affected by age or sex, but hemoglobin concentration definitely is, as are many other substances or functions. Because of the lack of specific information on normal distributions with regard to the many known and unknown variable factors, some hospitals specially designate only those values lying outside the upper and lower 2½% of all determinations in that hospital. This serves to alert the physician to his patient's differences from a specific population but does not identify the result in terms of normal or abnormal. In view of the indefinite status of "normality," this approach has certain merit as well as weaknesses.

Statistical Analysis

Statistics are important in the analysis and application of the data obtained. It is a statistical aphorism that no analysis is better than the data with which it deals. If the normal values are biased by sample selection, there is no statistical way to extrapolate meaningfully beyond the real population. Selected populations can be randomly or completely sampled, though, and the statistical manipulation of the data can make them more meaningful and more useful when applied to the base population or compared to a different one.

Normal Distribution

The concepts of the normal curve, the mean and the standard deviations are generally familiar to medical practitioners. Because there is an overlap in values between normals and abnormals, as previously discussed, the determination of abnormality cannot be based on a borderline level. As a matter of clinical judgement, the physician weighs the laboratory data with his own and other findings and either establishes or rejects a given diagnosis. He judges the value in terms of the probability that it might occur normally and, accordingly, he should be able to describe accurately the percentage of normal people who might be expected to yield such a value or a higher or lower one. A normal distribution curve that can be applied in this manner is the goal of many normal value studies. Since theoretically 95% of the larger population from which the group is drawn will fall within a range of ± 2 standard deviations, these are generally accepted as the working limits of the normal range. The benefits of this reasoning are well known and some of the pitfalls of poorly defined normal values have been indicated. What has not been mentioned is that *not all* laboratory values follow normal curve distributions and that in these instances other rules apply.

Log Normal Distribution

Henry[18] has emphasized that many biological phenomena vary according to an exponential function rather than arithmeti-

Continued

cally. Population values distributed in this manner show a skewed arithmetic curve, and applying normal distribution statistics to these data (unless they are transformed to the logarithmic function) leads to unreasonable and unmeaningful results. "Normal values" analyzed improperly are not only meaningless but can be grossly misleading.

Multivariate Analysis

The laboratory diagnostic aids usually concern only one or two variables in terms of their interrelationships. Lindberg[19] has demonstrated an approach to the analysis of routine laboratory data with electrolytes that consider the simultaneous variation of four separate parameters, and biostatisticians have the tools to analyze simultaneously even more variables.

In the brave new computerized world it may be possible to characterize a previously occult disease syndrome by its laboratory profile in "ten-dimensional space." The most highly developed computer, man's own brain, deals with multiple variants in the diagnostic process. When automated laboratory facilities can be coupled with electronic data processing, the diagnostician's insight should be extended to new horizons with clearly defined, unambiguous ranges of normal values by which to judge his individual patient.

Summary

Normal values are fundamental to the practice of medicine. A clear definition of the basis on which they are gathered and the mathematical extrapolations and limitations to which they are subjected are necessary for best utilization. The increasing accuracy and precision of the individual laboratory measurement will become more meaningful when a corresponding degree of care is taken to formulate the scale against which values must be compared. Activity and progress in this field are increasing. Elsewhere it has been suggested that each community can be active in accumulating its own normal value data. Well-practiced laboratory medicine, intelligent statistical analysis and electronic computational tools are leading to new concepts and applications in this area.

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Your Age

A person's age is not dependent upon the number of years that have passed over his head, but upon the number of colds that have passed through it. — Shirley Wynne

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Our names are labels, plainly printed on the bottled essence of our past behavior.
— L. P. Smith

Medical Technology Education*

RUTH F. HOVDE**
Minneapolis, Minnesota

IN THE LAST 42 years there have been 1,338 graduates of the University of Minnesota with Medical Technology degrees. The curriculum was originally under the jurisdiction of a committee of the Medical School composed of Dr. S. Marx White, Dr. Wilfred Larsen, and Dr. Richard Beard. The four-year degree program, the first of its kind in the United States, was, at that time, a daring innovation. In 1925 Dr. William O'Brien took over the chairmanship of the committee. Under his leadership the curriculum content and clinical training expanded and became more clearly defined.

In 1940 Dr. Evans assumed responsibility for directing the program. Through his abilities, creativity, imagination, and understanding of people the school became nationally recognized as a leader in the education of medical technologists. He repudiated the apprenticeship system which was dominated by the service demands of the hospital. He demanded quality in the courses given and in the faculty that taught them. He led the struggle for the national minimum requirement of four years of education at the college level for certification as a medical technologist. Today universities and hospital schools throughout the country use the curriculum and practices set forth by Dr. Evans.

He foresaw that the growth and utilization of the clinical laboratory would result in a shortage of technologists. To forestall this he helped set up the first program for medical laboratory assistants. To date 378 students have completed the course. Of these, 76% are still in the working force, primarily in hospital laboratories and physicians' offices. There are now 77 schools approved for training medical laboratory assistants in

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*Abstract of a paper presented at the staff meeting of the University of Minnesota Hospitals and Medical School on November 20, 1964.

**Professor and Director, Division of Medical Technology, Department of Laboratory Medicine, University of Minnesota.

Continued

the United States, their curriculums largely guided by the experiences and programs established here.

In order that Medical Technology flourish, Dr. Evans recognized the need for continuation of education beyond the B.S. degree. In 1960 he helped establish a graduate program in medical technology leading to a Master of Science degree and providing the opportunity for technologists of superior ability to continue academic work under the auspices of the Graduate School. To date, four students have completed the Master's program. All four are in educational programs in schools of Medical Technology.

As a young profession Medical Technology is faced with difficult problems in education brought about by increasing complexities and demands in the clinical laboratory. Historically, laboratory personnel were trained on the job as assistants or as apprentices in private hospitals, with no standardized curricula or basic academic preparation. The purpose of the training programs, if they could be called that, was to ensure a supply of future workers. The students were taught only "know-how," in the belief that methods would not change during their working lifetime. But methods did change, and the laboratories found their technicians could not adjust.

A national concern by medical educators developed over the poor quality of Medical Technology education. The hospitals turned to the colleges and universities for academic affiliation, and it became apparent that a standardized curriculum was needed.

As medical educators in the Universities and Medical Centers we must recognize our responsibilities in educating medical technologists. Should the onus for education rest on the medical schools, or will hospital laboratories continue to play the dominant role? The hospital's task is primarily to provide care for the sick. Training medical technologists is a job for which hospitals never were intended. Their educational programs — the product of the apprentice system — often are not systematic or broad. Cognizance must be given to an organized, rounded, and academic approach in teaching.

Hospital schools are forced to limit their techniques to those demanded by the service needs of the hospital. They cannot, in the twelve-month period allotted to their programs, cover the spectrum of techniques and instruments used in the modern clinical laboratory. One survey reported that the technologist in a modern hospital laboratory performs as many as 871 functions, falling into 19 categories. In these circumstances it is impossible to learn both theory and techniques.

How can a balance between knowledge and application of basic sciences be achieved in a college curriculum? Will learning practical technique be included in the training? The function of higher education is to provide the ability to understand theory so that practical skills can be attained later. The programs must include a broad approach to science with emphasis on the creative application. The technologist must have responsibility for the application of knowledge in the laboratory; he must have creativity, ability, and flexibility. To produce these persons the program of education must be reappraised.

Will extension to a five-year program be the answer in Medical Technology? It could be. But what about money for students in such a course? At the present time, salaries for the graduate medical technologist will not lure many students into a five-year course. Medical Technology attracts mostly young women, and women are not inclined to spend five years in a collegiate program.

But demands for laboratory services are increasing, and the problems of the medical technologist's education must be resolved. Among these problems are: (1) Automation — Automation is rapidly approaching, but small hospitals do not yet have the volume to warrant investment in automated equipment. Therefore, we must give students experiences with both hand methods and automated methods. (2) Specialization — With complexity comes fragmentation into special fields. Should the university produce specialists or generalists? Small hospitals cannot support a staff of specialists, and the generalist will continue to be dominant — especially during the night shifts. (3) The gifted students — How can the talents of the gifted student be used? Presently, requirements and standards are geared to the average. Bright students should be encouraged to go to graduate school and to enter into teaching or research in Medical Technology. (4) Continuing education — To keep up with advances in technology, especially in instrumentation, refresher courses must be given.

I hope I have brought into focus some of the problems of medical technology education. These would have been much greater if it had not been for the accomplishments and vision of Dr. Evans.

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*Papyrus Ebers**

For 'Tremblings'

For the ancient Egyptian afflicted with 'tremblings' there were available the following incredible remedies:

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Caraway
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Excrement-of-the-Gods
Honey
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Fresh Lead-earth
Cook into one and apply as a Poultice

To Drive Away Tremblings in all the Limbs of a Person

Fruit-of-the-Dompalm
Garlic
Honey
Copper
Verdigris

Put a Dog's Hide on Him!
*Do Not Press the Hand on Him!***

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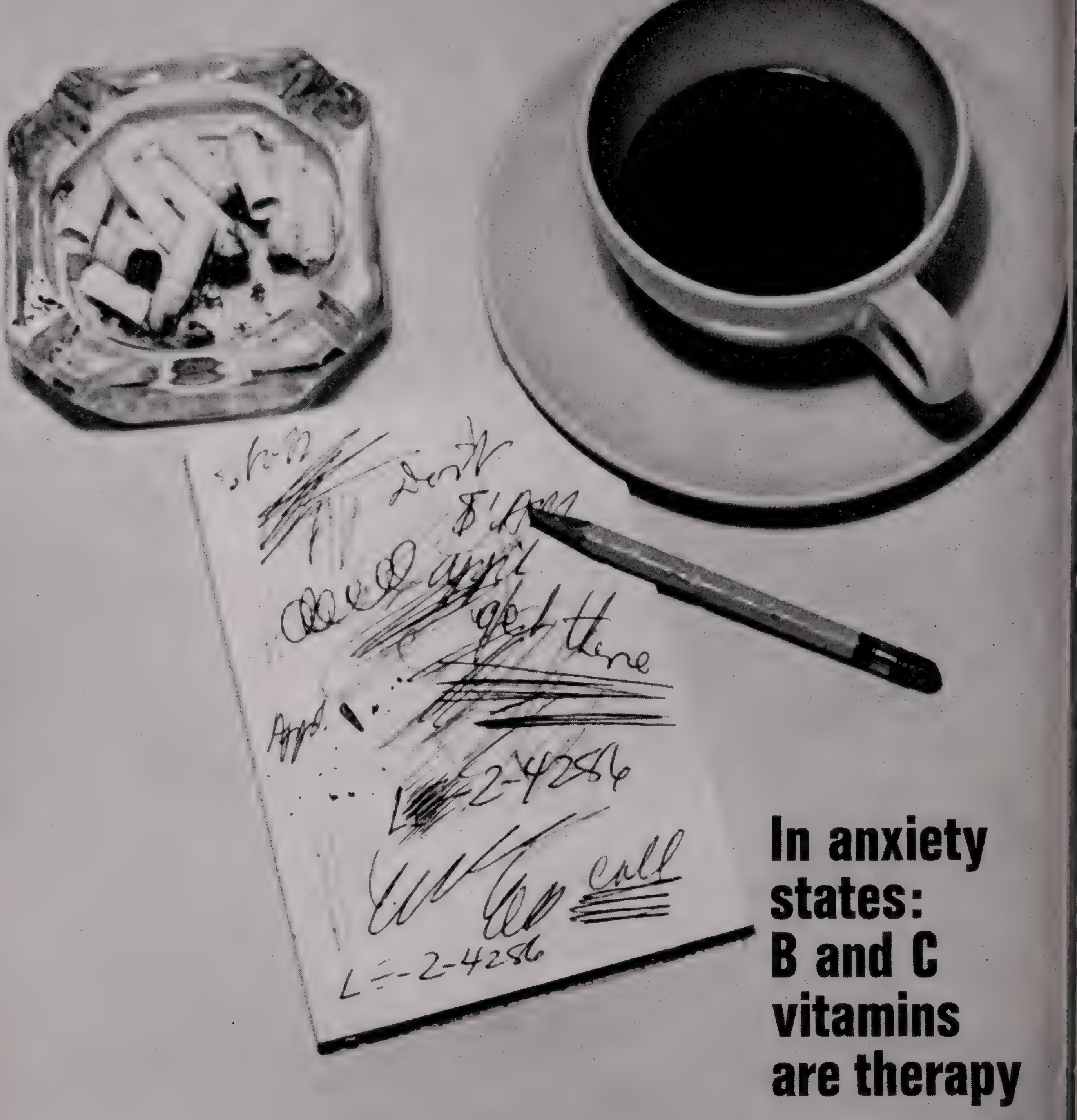
*See Minnesota Med 48:1468, 1576 and 1694, 1965, and 49:124, 433, 1966.
**Bryan, Cyril: The Papyrus Ebers, D. Appleton and Company, New York, 1931, p. 63-64.

Strange that rival political candidates think it necessary to invent lies about each other when the plain truth would probably be bad enough.

— Boston Shoe and Leather Reporter



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History of Medicine

The Discovery of Insulin

Part II

I think it is pertinent to the story of the discovery of insulin to clarify at this time what there was in the article in the issue of "Surgery, Gynecology and Obstetrics" of November 1920 that so sparked the imagination of Dr. Banting that he could not sleep that night, as he tells it, for pondering on the new ideas suggested to him by this article. He found here a wholly new approach: how one might obtain the hormone which appeared to control carbohydrate metabolism, freed from the contaminating digestive ferments which ordinarily are present in the pancreatic extract, when the pancreatic duct has not previously been ligated.

This problem of how to cope with the presence of the protein-digesting ferments in the extracts of the pancreas, which destroy the antidiabetic hormone of the Islets, since it is a protein and therefore subject to digestion, had previously frustrated researchers for more than 25 years before Banting's time.

The article which Dr. Banting referred to described a case which I had observed at postmortem, in which the pancreas was most unusual. Though the length was normal, its thickness was reduced to about one third of the normal measurement, and instead of being solid, on cross-section it was found to be hollow, containing fluid and giving the appearance of rubber tubing. At the lower end it was filled with pancreatic stones, completely obstructing the duct. Microscopic sections showed the wall to be composed of scattered Islets of Langerhans imbedded in scar tissue with some inflammatory cells. There were no acinar cells present, which produce the digestive ferments. The striking feature of this microscopic picture was the complete absence of those cells which secrete the digestive juices; whereas the Islet cells were practically intact. Clinically there was no evidence of diabetes.

This condition impressed me as being so unusual that I reviewed the literature on the subject and became especially interested in the histopathology that had been found in experimental ligation of the pancreatic ducts in animals.

I noted in the literature that surgical ligations of the pancreatic ducts in animals produced findings almost identical with those I had noted in this autopsy. An example of this is to be found in the experiments of Sobolew, who in 1902 ligated the pancreatic ducts in rabbits, cats, and dogs, and found that following the ligation of the ducts there was atrophy and sclerosis of the pancreas, unaccompanied by glycosuria. Microscopically, the Islets remained practically intact. Similar results from ligating the ducts had been obtained by Kamimura. In 1917 when he ligated the ducts in 100 rabbits, he found that at the end of the second week the normal structure of the cells had been so altered that they were scarcely identifiable as pancreatic tissue, and that, during the fifth week, very few nests of parenchymal cells were visible. The entire organ had been replaced by scar tissue, but the Islet cells were still intact. However, the examination of the blood and urine had shown neither hyperglycemia nor glycosuria.

From this Kamimura concluded that the Islets controlled carbohydrate

Continued

metabolism through the production of some internal secretion, and that destruction of the glandular portion of the organ through ligation was in no way connected with the utilization of sugar. It was the description of these experiments and of others of similar character, together with the description of that very rare and unique condition of the pancreas found at the postmortem I had performed, that led Banting to realize the possibility of obtaining by ligation an antidiabetic hormone from the pancreas, free from admixture of the enzymatic secretion which is bound to destroy the antidiabetic hormone by digestion and also to prove toxic on injection.

It was the revelation of this fact which immediately excited Dr. Banting to conceive the idea of the possibility of attacking the problem of how to obtain a pure secretion of the Islet cells for the treatment of diabetes. To quote Dr. Banting's words, "It was not until 2 o'clock in the morning that I was able to crystallize the idea into a form that would lend itself to experimentation."

This is the story of the discovery of insulin by Dr. Banting.

It is impossible to estimate the far-reaching results of this great boon to mankind, the lives it has saved, the suffering it has spared. Today there are in this country alone two and a half to three million diabetics, for more than half of whom life has been prolonged and living made more comfortable through the use of insulin.

In his short life of fifty years (1891-1941) Dr. Banting was able to do so much for mankind.

I would like to pay my personal tribute to Doctor Banting as a man, for I believe he showed greatness in the way he unstintingly, in his writings and in his lectures, acknowledged the fact that his discovery followed the reading of my article. Such forthrightness is not to be taken for granted.

Moses Barron, M.D.*
Minneapolis, Minnesota

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*Professor Emeritus, Medical School, University of Minnesota.

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The Delight of Victory

There takes place between a disease and a doctor . . . such a struggle as doctors alone know. The reward for it, should it be successful, is never the venal fee, nor even anything that happens to the patient. It consists in a pleasant satisfaction of mind and in some sort of ideal and invisible laurel, such as is gained by any true artist who is certain that he has done a good work. The physician strives for the good as the artist strives for the beautiful, each pushed on by that admirable feeling we call virtue.

— Honore de Balzac (1799-1850)

113th Annual Meeting

Call to Order

Annual Meeting Events Highlighted

W-e-l-c-o-m-e to St. Paul! Your host members of the Ramsey County Medical Society welcome all Minnesota physicians and their wives to attend the 113th Annual Meeting of the Minnesota State Medical Association, May 16 and 17 in St. Paul.

The 1966 scientific sessions will be held at the St. Paul Municipal Auditorium. The House of Delegates will convene Sunday, May 15 at 2:00 P.M. at the St. Paul Hotel.

American Medical Association President, Dr. James Z. Appel, will address delegates at their opening session on Sunday, May 15. He will also be the speaker at the new members, county officers, and delegates dinner on Sunday evening. The House will reconvene Tuesday, May 17 at 9:00 A.M.

Pre-registration for attendance at this year's meeting has been recommended by the Committee on Scientific Assembly. Registration materials have been included with earlier mailings of the Executive Secretary's Newspage for your convenience. By preregistering before May 10, physicians will be assured that their badges will be waiting for them at the advance registration desk at the St. Paul Auditorium.

Physicians are also urged to use the card enclosed with advance registration materials to make room reservations early.

Register or secure your badge at the registration desk in the St. Paul Municipal Auditorium on Monday, May 16 from 8:45 A.M. to 5:15 P.M., and Tuesday from 8:45 A.M. to 5:15 P.M.

Advance registration for the Round Table Luncheons Monday and Tuesday noon is desirable. Tickets should preferably be purchased in advance by completing and returning the advance registration cards enclosed with the official annual meeting program mailed to all members. Round Table Luncheon tickets may also be purchased at the St. Paul Auditorium registration desk. As in the past, latecomers will be accomodated according to their choice if luncheon limits have not already been reached.

The annual banquet on Tuesday, May 17 will be preceded by a social hour at 6:00 P.M. Banquet activities will feature outstanding entertainment, including a floor show and dancing.

Fifty club members will be honored guests and a medal for the outstanding scientific exhibit will be presented by the Southern Minnesota Medical Association.

For golfers there will be the annual tournament on Sunday, May 15 at the White Bear Yacht Club. The tournament will be followed by a 6:15 P.M. golfers dinner to which all members of the Association and their wives are cordially invited.

The Minnesota State Medical Association Fourth Duplicate Bridge Tournament is scheduled to begin Monday at 9:00 P.M. at the St. Paul Hotel. The tournament is open to all bridge players and duplicate experience is not necessary.

Among the many excellent features on this year's Scientific Assembly Program will be a discussion on the "Prevention and Treatment of Knee Injuries in the Athlete." This discussion is scheduled for 11:00 on Tuesday, May 17, and will include a paper by Dr. Harvey O'Phelan, Minneapolis. Professor Lloyd Stein of the University of Minnesota Athletic Department will demonstrate the

Continued

taping of injuries.

The Minnesota Society of Clinical Pathologists will hold a one day session in conjunction with the annual meeting, beginning at 9:00 A.M., Monday, May 16, in the Minnesota Club.

The Minnesota Academy of General Practice will hold its annual banquet on Monday evening.

Other organizations and specialty groups which have scheduled events in conjunction with the meeting include the Minnesota Radiological Society, Twin Cities Diabetes Association, Minnesota Chapter, American College of Chest Physicians, Minnesota Chapter of American Academy of Pediatrics, Minnesota Academy of Ophthalmology and Otolaryngology and The Medical Women's Association.

To help physicians become better acquainted with the provisions of PL 89-97, the Minnesota State Medical Association will present a special program on Medicare Wednesday, May 18, at 9:00 A.M. in the St. Paul Hotel, the day immediately following the close of our Annual Meeting. The program will feature representatives of HEW, AMA, the Minnesota Department of Public Welfare, who will explain and answer questions about the operation of Medicare. Because the program has been particularly arranged to meet the needs of the physician in his daily practice, all physicians are urged to make plans now to attend our Annual Meeting, including this important seminar.

Committee breakfasts have been scheduled by many of the scientific and non-scientific committees. Members are urged to attend and participate in the activities of their respective committees also.

Scientific Program

Saint Paul Auditorium

MONDAY MORNING, MAY 16, 1966

The program on Monday is acceptable for 4½ accredited hours by the American Academy of General Practice.

A.M. Visit scientific and technical exhibits

9:00 **COMPUTER MEDICINE: ITS APPLICATION TODAY AND TOMORROW**
Morris F. Collen, Oakland, California

9:40 **WHAT'S NEW IN HEMATOLOGY?**
A. B. Hagedorn, Rochester

10:15 Visit scientific and technical exhibits

11:00 **OBSTRUCTIVE RESPIRATORY DISEASES**
William R. Fifer, Minneapolis
Moderator
Norman G. Hepper, Rochester
James P. Lillehei, Minneapolis
Frank M. MacDonald, Minneapolis

MONDAY AFTERNOON

P.M.

12:15 **ROUND TABLE LUNCHEONS**

1:30 Visit scientific and technical exhibits

2:00 **TREATMENT OF BURNS**
Carl A. Moyer, Houghton, Michigan

2:30 **PANEL ON THE DYING AND THE DEAD**
Harold W. Hermann, Minneapolis
Moderator
Bishop James P. Shannon, St. Paul
Chairman
Rev. Elmer Hjortland, Oak Park, Illinois
Rabbi Albert G. Minda, Minneapolis

3:30 Visit scientific and technical exhibits

4:00 **RESPIRATORY DISTRESS SYNDROME IN THE NEWBORN**
Mary Ellen Avery, Baltimore, Maryland
Martha B. Strickland, St. Paul
Discussant

TUESDAY MORNING, MAY 17, 1966

The program on Tuesday is acceptable for 4½ accredited hours by the American Academy of General Practice.

A.M. Visit scientific and technical exhibits

9:00 **ISOTOPES AS A DIAGNOSTIC TOOL**
Paul V. Harper, Chicago, Illinois

9:40 **DIAGNOSIS AND TREATMENT OF HYPERTHYROIDISM**
L. O. Underdahl, Rochester

10:15 Visit scientific and technical exhibits

11:00 **PREVENTION AND TREATMENT OF KNEE INJURIES IN THE ATHLETE**
Harvey O'Phelan, Minneapolis
Professor Lloyd Stein, University of Minnesota

TUESDAY AFTERNOON

P.M.

12:15 **ROUND TABLE LUNCHEONS**

1:30 Visit scientific and technical exhibits

2:00 **JUVENILE DIABETES**
Priscilla White, Boston, Massachusetts
Donnell D. Etzwiler, Minneapolis
Discussant

TUESDAY AFTERNOON CONTINUED

2:30 **MANAGEMENT OF STREPTOCOCCAL AND STAPHYLOCOCCAL INFECTIONS: NEWER CONCEPTS**
Donald R. Nichols, Rochester

3:00 Visit scientific and technical exhibits

3:30 **THE EARLY RECOGNITION AND PREVENTION OF BLINDNESS**
Robert Hugh Monahan, St. Paul

4:00 **THE OB-GYN SEMINAR**
"Endometriosis, the Conservative vs. the Radical Surgical Treatment"
Bruce F. P. Williams, Duluth
"*Early* Invasive Carcinoma of the Cervix"
John M. McKelvey, Minneapolis
Joseph H. Pratt, Jr., Rochester

TUESDAY EVENING

7:00 **ANNUAL BANQUET**
Reception
Presentations
Entertainment, Dancing and Late Evening Buffet

Round Table Luncheons

Saint Paul Hotel

MONDAY — 12:15 P.M.

Fluids in Infancy
Mary Ellen Avery, Baltimore, Maryland

The Spiritual Dimension of Suffering
Harold W. Hermann, Minneapolis
W. F. Widen, Minneapolis

The Use of Saline Solutions in the Treatment of Hemorrhagic and Traumatic Shock
Carl A. Moyer, Houghton, Michigan

Treatment of Leukemia
A. B. Hagedorn, Rochester

Management of Emphysema
William R. Fifer, Minneapolis

Computers in Preventive Medical Research
Morris F. Collen, Oakland, California

TUESDAY — 12:15 P.M.

Prevention and Treatment of Ankle Injuries
Professor Lloyd Stein, Minneapolis

Value and Use of the Tonometer
Robert Hugh Monahan, St. Paul

The Brittle Diabetic
Priscilla White, Boston, Massachusetts

Radioactive Isotopes in Clinical Practice
Paul V. Harper, Chicago, Illinois

Amniocentesis, A Diagnostic and Therapeutic Tool
Bruce F. P. Williams, Duluth

Therapeutic Abortion in General and in Rubella
John M. McKelvey, Minneapolis

Program Highlights

. . . Dr. James Z. Appel, President of the American Medical Association, will address the House of Delegates at their opening session on Sunday, May 15. He will also be the speaker at the New Members, County Officers and Delegates dinner on Sunday evening.

. . . Please reserve Wednesday, May 18, following the annual meeting for a seminar on Medicare at the Saint Paul Hotel, beginning at 9:00 a.m. Representatives of HEW, AMA, the Travelers Insurance Company, the Minnesota Welfare Department, and other officials will discuss the many facets of Medicare, including Title XIX.

. . . For golfers — The annual golf tournament will be held on Sunday, May 15, at the White Bear Yacht Club followed by a dinner at 6:15 p.m. to which all members of the Association and their wives are cordially invited.

. . . Special attention is called to the day-long session on Monday of the Minnesota Society of Clinical Pathologists which begins at 9:00 a.m. at the Minnesota Club and continues through 4:30 p.m. The program will include a symposium on "Evaluation of Thyroid Function," and beginning at 2:00 p.m. "Case Reports" with panelists.

. . . Advance registration card for the meeting and the card for hotel accommodations were sent to all members with the Association's March newsletter. Use of these cards will save you time and greatly facilitate your attendance at the meeting.

. . . All high school coaches in the Twin Cities and surrounding area have been invited to hear Dr. Harvey O'Phelan and Professor Lloyd Stein discuss "Prevention and Treatment of Knee Injuries in the Athlete," a highlight of the Tuesday morning scientific session.

. . . The Association's 4th duplicate bridge tournament will begin at 9:00 p.m. on Monday night at the Saint Paul Hotel. It is open to all bridge players, duplicate experience is not necessary.

You are today where your thoughts have brought you; you will be tomorrow where your thoughts take you. — The Gilcrafter

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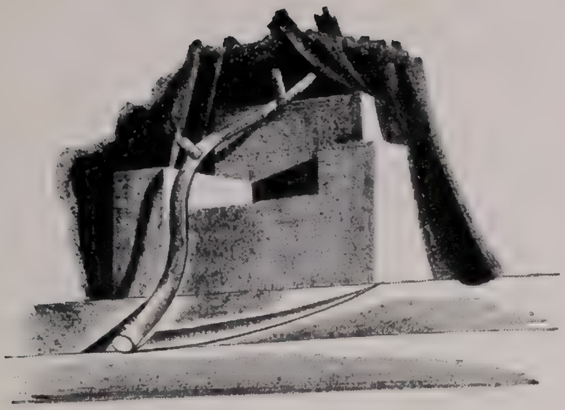

In Memoriam

If thou expect death as a friend, prepare to entertain him; if as an enemy, prepare to overcome him. — Death has no advantage except when it comes as a stranger.
— Quarles

GEORGE L. JOYCE, M.D.

Dr. George L. Joyce, 64, Rochester physician, died March 8. He was born in Stewartville, Minnesota, and obtained his medical degree from Loyola University Medical School in Chicago. Before going to Rochester in 1935 to open up his practice, Dr. Joyce practiced in Stewartville. He was the Olmsted County deputy coroner for the past twelve years.

Dr. Joyce was a member of the Rochester Council 1013, Knights of Columbus, a member of the Zumbro Valley Medical Society, American Medical Association and Minnesota State Medical Association.

He is survived by his wife and a daughter.

FREDERIC E. B. FOLEY, M.D.

Dr. Frederic E. B. Foley, 74, St. Paul urologist, died March 24. He was born at St. Cloud and graduated from Yale University and Johns Hopkins Medical School. Early in his career, Dr. Foley was assistant pathologist at Johns Hopkins and conducted research for several years in Boston, Massachusetts.

In 1920 he established the Department of Urology at Ancker Hospital and was chief of the department until 1964. Dr. Foley invented the self-retaining bag catheter, which bears his name, in 1929 and devised a kidney surgical procedure now considered classical in urological surgery.

The American Academy of Arts and Sciences in 1955 awarded Dr. Foley the Francis Amory Septennial Award for his outstanding contributions to urology. He was a former professor of clinical urology at the University of Minnesota Medical School and practiced medicine in St. Paul from 1922 to 1960. The St. Paul-Ramsey Hospital department of urology is named in his honor.

Dr. Foley was a member of the Ramsey County Medical Society, American Medical Association and associate member of the Minnesota State Medical Association.

He is survived by a daughter.

LAWRENCE JENS KAASA, M.D.

Dr. Lawrence J. Kaasa, 86, former physician in St. Peter, died February 22. He was born in Winneshiek County, Iowa, and obtained his medical degree at the State University of Iowa, College of Medicine.

He was a member of the Freeborn County Medical Society and American Medical Association and was a 50 Club and associate member of the Minnesota State Medical Association.

He is survived by his wife and three children.

GUNNAR LINNER, M.D.

Dr. Gunnar Linner, 61, Richfield physician, died March 25. Born in Waltham, Massachusetts, Dr. Linner received his medical degree at the University of Minnesota. In 1930 he was the Stillwater prison doctor, and later headed the Anoka state hospital. Also, Dr. Linner was the physician at the Minnesota Masonic home at Savage.

He was a member of the Hennepin County Medical Society, the American Medical Association and the Minnesota State Medical Association.

He is survived by his wife, a son and a daughter.

L. WILLIAM MORSMAN, M.D.

Dr. L. William Morsman, 82, Hibbing ophthalmologist, died March 25. He was born in Rising City, Nebraska, and graduated from the University of Nebraska, College of Medicine.

Dr. Morsman was one of the physicians responsible for organizing the medical society in the Iron Range Area forty-nine years ago. He not only was a member of that society but also was a member of the American Medical Association and a life and 50 Club member of the Minnesota State Medical Association.

JOHN WILLIAM EKBLAD, M.D.

Dr. John W. Ekblad, 91, a Duluth physician for forty-seven years and former St. Louis County coroner, died April 1 in Rock Island, Illinois, where he had resided for the past ten years. A native of Cleburne, Kansas, he graduated from the University of Kansas Medical School. He practiced medicine in Kansas until 1908 before coming to Duluth.

Dr. Ekblad retired from the practice of medicine

Continued

in 1955. He was a member of the St. Louis County Medical Society and American Medical Association, and a life and 50 Club member of the Minnesota State Medical Association. Dr. and Mrs. Ekblad would have observed their 65th wedding anniversary this summer.

He is survived by his wife and a son. Dr. Victor E. Ekblad of Superior is his brother.

HERBERT WILLIAM SCHMIDT, M.D.

Dr. Herbert W. Schmidt, 62, Mahtomedi physician and medical director of Minnesota Mining and Manufacturing Company, died April 6. A native of Northfield and a graduate of St. Olaf College, he received his doctorate in medicine from the University of Minnesota. Dr. Schmidt joined the Mayo foundation in 1934 as a fellow in surgery and was appointed to the Mayo Clinic staff in 1937. In 1948 he was named to head a section of medicine at the Clinic. He had served as president of the Clinic staff and as a member of its board of governors.

He also had served as professor of medicine at the Mayo foundation graduate school, University of Minnesota. Dr. Schmidt was a member of several professional and honorary societies including the Minnesota Thoracic Society, American Association for Thoracic Surgery, Ramsey County Medical Society, American Medical Association and Minnesota State Medical Association.

He is survived by his wife, a son and two daughters.

ALBERT L. PERTL, M.D.

Dr. Albert L. Pertl, 66, former Windom physician, died February 12. He was born in West Bend, Iowa, and obtained his medical degree from the State University of Iowa.

He practiced in Canby and was a member of the Canby school and library boards after the family left Windom twenty-eight years ago. He was a member of the Camp Release District Medical Society, American Medical Association and an associate member of the Minnesota State Medical Association.

He is survived by his wife and three children.

CHARLES N. SPRATT, M.D.

Dr. Charles N. Spratt, 91, formerly of Big Lake, Minnesota, died April 4 in Phoenix, Arizona. Born in LeSueur, he graduated from the Johns Hopkins Medical School.

He was a member of several professional societies including the Hennepin County Medical Society and American Medical Association, and was a life and 50 Club member of the Minnesota State Medical Association.

He is survived by his wife and four daughters.

ELWYN RAYMOND HUDEC, M.D.

Dr. Elwyn Ray Hudec, 55, who practiced medicine for twenty-eight years in Echo, died March 11. He was born in Winsted Township, McLeod County, graduated from Silver Lake high school and received his medical degree at the University of Minnesota.

Dr. Hudec was active in many civic and community projects, having served as mayor of Echo. He was a member of the Board of Education and the Lions International.

He was a member of the Camp Release District Medical Society, American Medical Association and Minnesota State Medical Association.

He is survived by his wife, a son and a daughter.

JOHN J. HOCHFILZER, M.D.

Dr. John J. Hochfilzer, 75, St. Paul ear, nose and throat specialist, died March 12, while on a skiing vacation in Colorado. Dr. Hochfilzer was clinical associate professor emeritus at the University of Minnesota school of medicine. He was on the staffs of St. Paul, Ramsey County and Miller hospitals.

Born in Elmau in the Tyrol in Austria, Dr. Hochfilzer received his medical education at the University of Innsbruck. He arrived here from Austria in 1923. He was the author of a number of articles in his field, and a member of the Academy of Otolarynology and the Triological Society. He was a member of the Ramsey County Medical Society, American Medical Association and a life member of the Minnesota State Medical Association.

He is survived by his wife.

"Man is of few days and full of trouble." Yet in the face of this acknowledged truth, he requests and expects that his physician will provide him with many days, and remove at least his bodily troubles.

Most men form an exaggerated opinion of the powers of medicine, founded on the common acceptation of the name, that medicine is the art of curing diseases. That this is a false definition, is evident from the fact that many diseases are incurable, and that one such disease must at last happen to every living man. A far more just definition would be, that medicine is the art of understanding diseases and of curing or relieving them *when possible*. Under this acceptation our science would at least, be exonerated from reproach, and would stand on a basis capable of supporting a reasonable and durable system for the amelioration of human maladies. — Jacob Bigelow (1787-1879)

Achievement

The world is not interested in the storms you encountered, but did you bring in the ship? — William McFee

Meetings and Announcements

After a spirit of discernment, the next rarest thing in the world is diamonds and pearls. — Bruyere

MAY

Hennepin County Medical Society meeting, May 2 at 6:00 p.m., Pick-Nicollet Hotel, Minneapolis.

Hennepin County Psychiatric Society meeting to be held in connection with Hennepin County Medical Society Meeting on May 2.

Minnesota Society of Internal Medicine meeting, May 3 at 9:00 a.m. in Minneapolis.

Minnesota Academy of Medicine meeting, May 11 at 6:30 p.m., Town & Country Club in St. Paul.

St. Louis County Medical Society Executive Committee meeting, May 12, at 6:00 p.m., and the regular meeting at 8:00 p.m., St. Mary's Hospital in Duluth.

Minnesota Society of Clinical Pathologists meeting during Minnesota State Medical Meeting in St. Paul.

Minnesota Obstetrical & Gynecological Society meeting to be held in Rochester at the Mayo Clinic. The date to be announced.

Radiology and Pathology Departments of University of Wisconsin postgraduate course on radiology and pathology of urinary system, May 4-6, Wisconsin Center, Madison, Wisc. Contact: Thomas Meyer, M.D., 432 N. Lake St., Madison

Symposium on the Battered Child, May 13-14, University of Colorado School of Medicine, Denver. Contact: Office of Postgraduate Medical Education 4200 E. 9th Avenue, Denver.

American Cancer Society scientific sessions, St. Francis Hotel, San Francisco, May 11. Contact: Director, 219 East 42nd Street, New York. Symposium will present advances in diagnosis of common cancer sites.

JUNE

Twenty-Third Annual Meeting American Geriatrics Society, Palmer House in Chicago, June 23-24. No registration fee: Contact: Edward Henderson, M.D., 10 Columbus Circle, New York.

Minnesota Academy of Medicine President's Meeting, June 8, Town and Country Club, St. Paul at 6:30 p.m.

St. Louis County Medical Society Executive Committee Meeting, 6:00 p.m., St. Luke's Hospital in Duluth, regular meeting, 8:00 p.m.

115th AMA Annual Convention, Chicago, June 26-30. Contact: AMA in Chicago for reservations.

ANNOUNCEMENTS

Dr. Birger Strandell, a member of the faculty of the Caroline Institute, Stockholm, and editor of ACTA MEDICA SCANDINAVICA, will lecture on "Linnaeus" at Rochester, May 10, 1966. The lecture, sponsored by the Mayo Foundation chapter of Sigma XI, will be held a day before the opening of the annual meeting of the American Association for the History of Medicine. Contact: Thomas E. Keys, 200 First Street Southwest, Rochester, Minnesota.

* * *

A symposium on Liver Disease will be held in the Mayo Auditorium of the University of Minnesota May 23, 24 and 25, in honor of Cecil James Watson, M.D. Symposium is open to all physicians at no charge.

* * *

Spring Cardiopulmonary Seminar will be held at Mount Sinai Hospital, May 19, 20. Contact: Jerome T. Grismer, M.D., Mt. Sinai Hospital, Minneapolis.

* * *

Minnesota State Medical Association Meeting, May 16-17, St. Paul Hotel, St. Paul. Contact: Harold W. Brunn, Executive Secretary, 496 Lowry Medical Arts Building, St. Paul.

* * *

One day educational program for physicians sponsored by Minnesota Heart Association, May 21, 8:30 a.m. at the Radisson Hotel in Minneapolis. Contact: Marie Nelson, 1821 University Avenue, St. Paul or Dr. Reuben Berman.

* * *

Minnesota Surgical Society Annual Essay Prize to be awarded in November, 1966. Prize of $500 will be given for the best paper on a surgical subject submitted by a medical student, intern or resident. Papers directed to surgical research and papers on clinical topics are acceptable. Deadline for submission of manuscripts is August 1, 1966. Send papers to: John F. Perry, Jr., M.D., St. Paul-Ramsey Hospital, 640 Jackson St., St. Paul.

Sustained circulatory, respiratory and cerebral stimulation for the

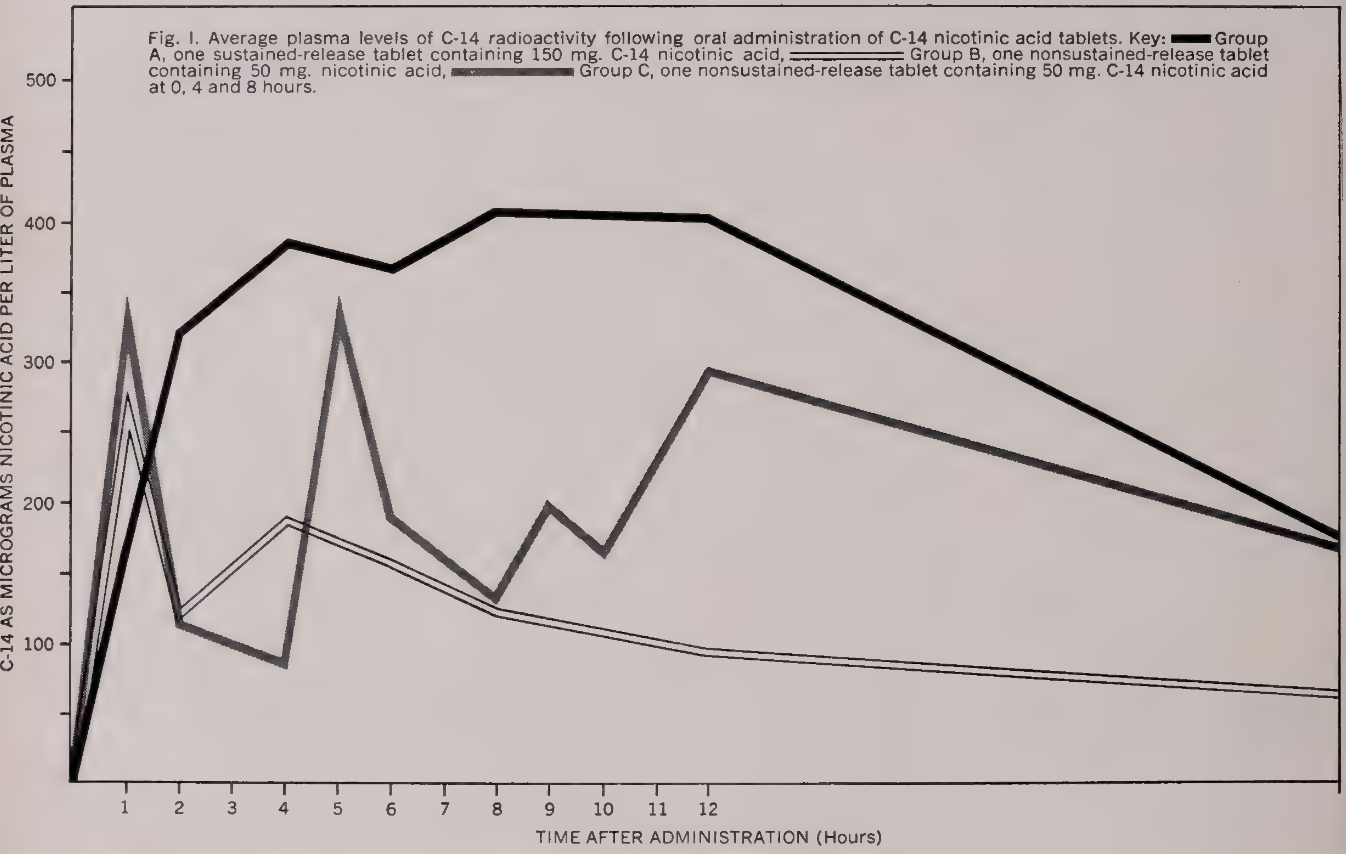

Fig. I. Average plasma levels of C-14 radioactivity following oral administration of C-14 nicotinic acid tablets. Key: ▬ Group A, one sustained-release tablet containing 150 mg. C-14 nicotinic acid, ═ Group B, one nonsustained-release tablet containing 50 mg. nicotinic acid, ▬ Group C, one nonsustained-release tablet containing 50 mg. C-14 nicotinic acid at 0, 4 and 8 hours.

(fewer absent doses by absent-minded patients)

Human volunteer subjects were administered Geroniazol TT tablets with the nicotinic acid component made radioactive with C-14. Plasma and urine samples were analyzed. (See Figures I and II) The radioactive tracer study substantiated the previous clinical evidence that the release of nicotinic acid from the Geroniazol TT tablet produced a gradual rise in plasma levels to a plateau for a total of 12 hours and more.

Such proven sustained activity makes the management of geriatric patients much easier by minimizing the possibility of neglected doses through absent-mindedness or senile confusion. Therapy *can* be continuous on a daily dose of only one Geroniazol TT tablet every 12 hours.

The gradual release of nicotinic acid in Geroniazol TT will provide the well-known peripheral vasodilatation needed in patients with deficient circulation and with a minimum amount (if any) of "flushing." Also, cerebrovascular circulation is complemented by pentylenetetrazol, long-established as a cerebral and respiratory stimulant.

Geroniazol TT improves the typical, unfortunate, signs of senile confusion. Patients become more alert,

aged and debilitated

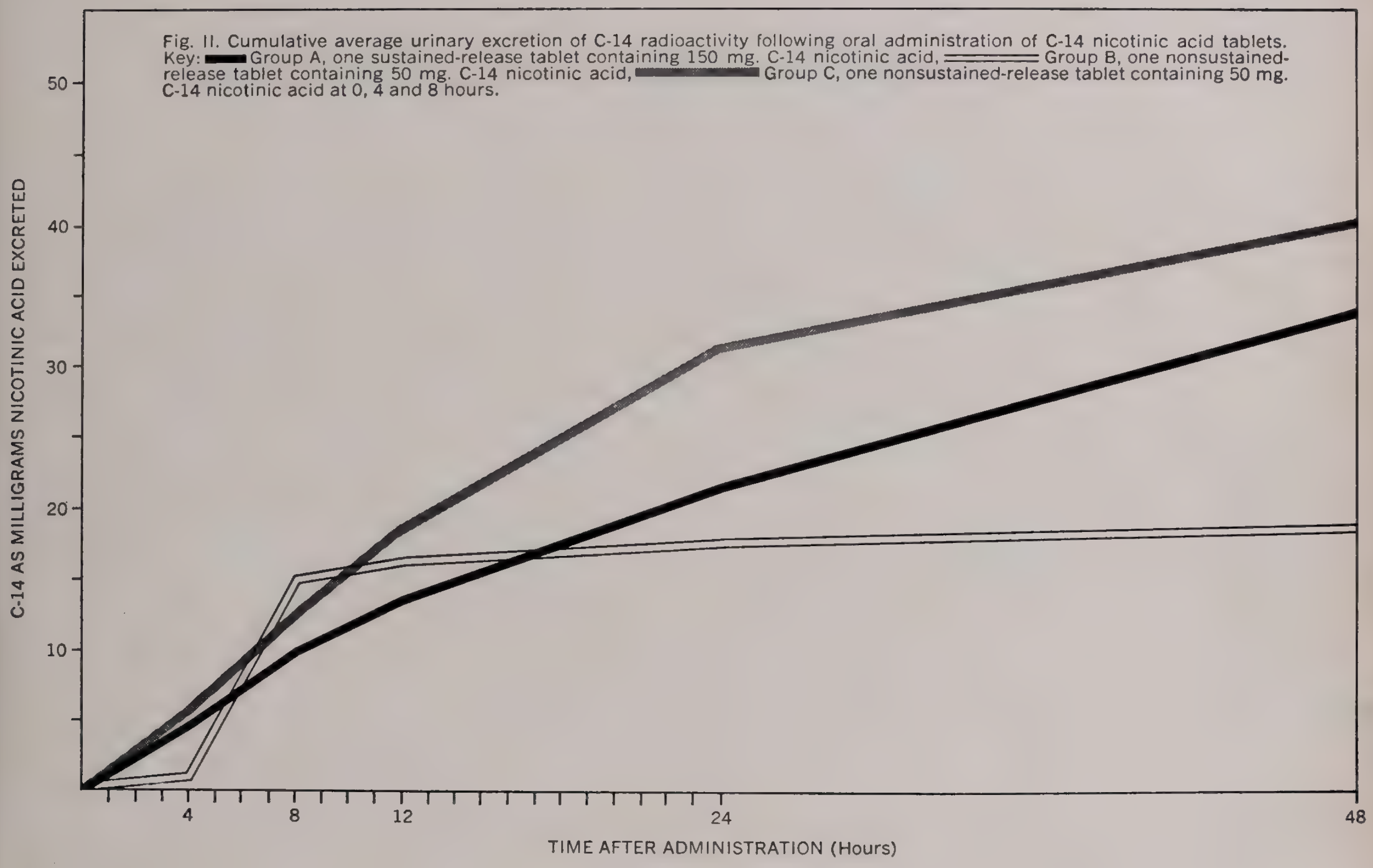

Fig. II. Cumulative average urinary excretion of C-14 radioactivity following oral administration of C-14 nicotinic acid tablets. Key: ━ Group A, one sustained-release tablet containing 150 mg. C-14 nicotinic acid, ═ Group B, one nonsustained-release tablet containing 50 mg. C-14 nicotinic acid, ▬ Group C, one nonsustained-release tablet containing 50 mg. C-14 nicotinic acid at 0, 4 and 8 hours.

less confused and moody. Personal care, memory, emotional stability, social attention improve. Fatigue, apathy and irritability are reduced.

A prescription for 100 tablets of Geroniazol TT will permit your patients to enjoy the benefits of time-prolonged nicotinic acid/pentylenetetrazol therapy, at an economical price. Dosage is only one tablet every 12 hours.

Contraindications: There are no known contraindications.

Precautions: Exercise caution when treating patients with a low convulsive threshold.

Side Effects: Side effects are rarely encountered, however due to the vasodilatation effect of nicotinic acid, transitory mild nausea, flushing, tingling and pruritus are possible.

Dosage: One tablet every 12 hours.

Supplied: Prescribe bottles of 100 tablets, to take advantage of recent price reduction.

References: 1. Report by Nuclear Science & Engineering Corp., Pittsburgh, Pa., in files of Philips Roxane Laboratories. 2. Connolly, R.: W. Virginia Med. J. *56*:263 (Aug.) 1960. 3. Curran, T. R., and Phelps, D. K.: Am. Pract. & Digest Treat. *11*:617 (July) 1960.

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PHILIPS ROXANE LABORATORIES
Division of Philips Roxane, Inc., Columbus, Ohio
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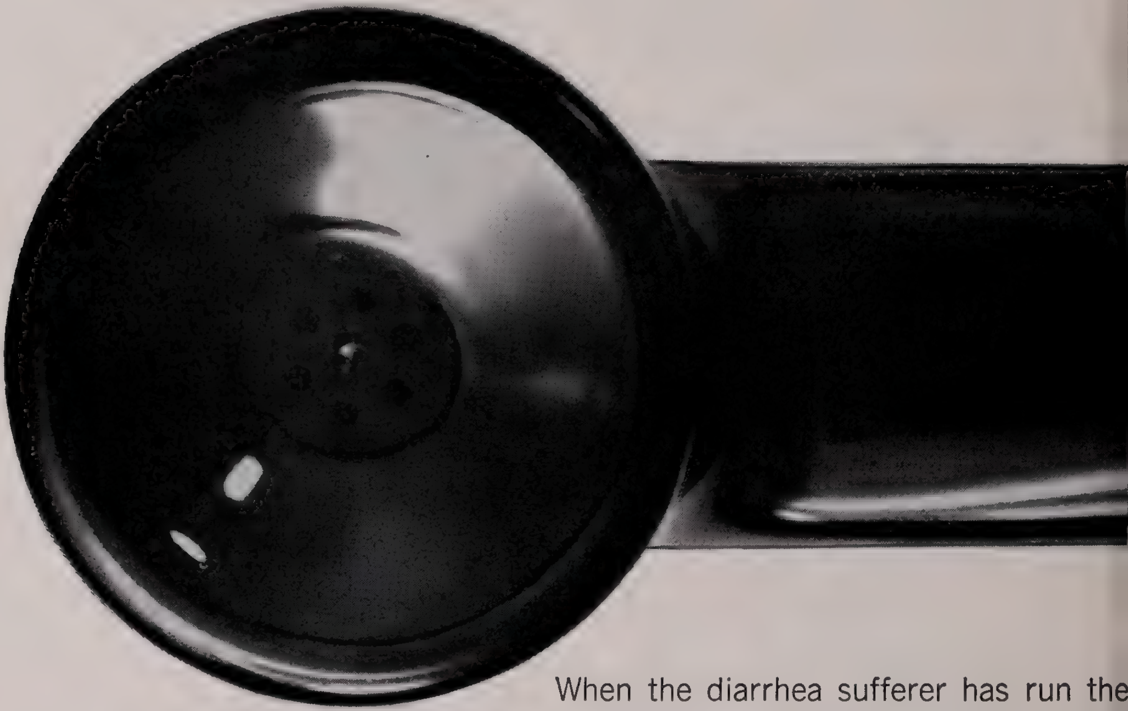
Geroniazol® TT

nicotinic acid 150 mg., pentylenetetrazol 300 mg.
Tempotrol® Time Controlled Tablet

When uncontrolled diarrhea brings a call for help



When the diarrhea sufferer has run the gamut of home remedies without success, pleasant-tasting CREMOMYCIN can answer the call for help. It can be counted on to consolidate fluid stools, soothe intestinal inflammation, inhibit enteric pathogens, and detoxify putrefactive materials—usually within a few hours.

CREMOMYCIN combines the bacteriostatic agents, succinylsulfathiazole and neomycin, with the adsorbent and protective demulcents, kaolin and pectin, for comprehensive control of diarrhea.

Indications: Diarrhea. *Contraindications:* Kaolin: Withhold if diverticulosis is present or suspected. *Precautions:* Sulfonamide: Continued use requires supplementary administration of thiamine and vita-

your ℞ for
Cremomycin
can provide relief

in K. Neomycin: Patient should be observed for ew infections due to bacteria or fungi. *Side Effects:* ulfonamide: Sensitivity reactions may occur (e.g., kin rashes, anemia, polyneuritis, fever; agranuloytosis with a fatal outcome has been reported). eduction of thiamine output in the feces and of itamin K synthesis has been observed. Neomycin: lausea, loose stools possible.

efore prescribing or administering, read product ircular with package or available on request.

romptly relieves diarrheal distress

Cremomycin®

ANTIDIARRHEAL

Composition: Each 30 cc. contains neomycin sulfate 00 mg. (equivalent to 210 mg. of neomycin base), uccinylsulfathiazole 3.0 Gm., colloidal kaolin 3.0 m., pectin 0.27 Gm.

MERCK SHARP & DOHME Division of Merck & Co., Inc., West Point, Pa.

here today's theory is tomorrow's therapy

Classified

Classified advertising rates are twenty (20) cents a word; minimum monthly charge $5.00; key number, fifty (50) cents additional.

Replies to advertisements with key numbers should be mailed in care of MINNESOTA MEDICINE, *496 Lowry Medical Arts Bldg., St. Paul, Minn. 55102*

WANTED: General Practitioner who is interested in general practice and surgery to associate with a small group in West Central Wisconsin. Salary and partnership open. Write: MINNESOTA MEDICINE — 349, 496 Lowry Medical Arts Building, St. Paul 55102.

INTERNIST for 20-physician-clinic in prosperous Minnesota city. Salary negotiable first year, then full partnership. East Range Clinic, Virginia, Minnesota.

LOCUM TENENS wanted for general practice, six-man, Twin City group, from now through summer 1966. Write: MINNESOTA MEDICINE — 345, 496 Lowry Medical Arts Building, St. Paul 55102.

WANTED: young radiologist, board certified or eligible to join five man group consisting of four GP's and a general surgeon. University town of 6,000 in Northwestern Wisconsin close to Twin Cities. Salary open with early partnership. Write: MINNESOTA MEDICINE — 347, 496 Lowry Medical Arts Building, St. Paul 55102.

GENERAL PRACTITIONER to join active six-man, AAGP, two office group. Liberal vacation, rotating night call, life insurance. Metropolitan area, salary leading to partnership. Write: MINNESOTA MEDICINE — 346, 496 Lowry Medical Arts Building, St. Paul 55102.

PSYCHIATRIC RESIDENCIES positions available July 1, 1966 for a three year accredited program. A dynamically-oriented broadly-based well-balanced opportunity for sound training. Meadowbrook Hospital is Nassau County General Hospital and is centrally located in the most desirable and beautiful area in the country. Easy commuting distance to New York City. 2600 in-patient psychiatric admissions per year, 24 hour walk-in clinic, and all psychiatric modalities. Abraham S. Lenzner, M.D., Director Psychiatric Education, Meadowbrook Hospital, P.O. Box 175, East Meadow, New York 11554.

PART TIME INTERNIST OR GENERAL PRACTITIONER. Good compensation — Midway Area. Alfred F. Anderegg, M.D.; 2500 Como Avenue, St. Paul, Minnesota.

WANTED: Board Certified or eligible internist to associate with group in large, active practice in Minneapolis. Group consists of Surgeon, Obstetrician, Pediatrician and Internist maintaining downtown and suburban offices. Partnership in mind. Contact: Jesse J. Barron, M.D., 1127 Medical Arts Building, Minneapolis, Minnesota 55402, FEderal 2-8259.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with early partnership. Write: MINNESOTA MEDICINE — 289; 496 Lowry Medical Arts Building; St. Paul, 55102.

OFFICE SPACE now available in busy Bloomington. 713 square feet of new space in building with busy group of G.P.'s, dentist and suburban OB-GYN office. Ideal for ophthalmology, ENT or pediatrics. 8040 Penn Avenue South. 888-9211.

GENERAL PRACTITIONER WANTED: to associate with physician-surgeon in Owatonna, a Southern Minnesota community, 25,000 population. Clinic building three years old; with five large treatment rooms, lab.; x ray; central supply; two doctors' offices; pharmacy; and business offices. Located next door to 85-bed city hospital. Good opportunity for partnership. Contact: O. W. Roberts, M.D.; 920 South Cedar Street; Owatonna, Minnesota. Phone 451-4630.

WANTED — Internist, board certified or qualified, to associate with two board certified internists. Ten man multi-specialty group. (Lenont Peterson Clinic, Virginia, Minnesota) — Heart of the expanding taconite industry.

FOR RENT: Successful medical building. Will help doctor or group of doctors get started in proven location in Northwest Suburban Minneapolis, 36th and Noble near two hospitals. Call or write Noble Drug, 4705 36th Avenue North, Minneapolis 22. Ju 8-9449.

WANTED: young general practitioner to join six-man group consisting of 4 GPs, a general surgeon, and radiologist. College town of 5,500, 30 miles from Twin Cities. Also need LOCUM TENENS in general practice. Contact: Ed Jenkins, Mgr., River Falls Medical Clinic, River Falls, Wisc. Phone 425-5322.

WANTED: Immediate opening for young GP in an established medical corporation. Three man G.P. group located in rapid-growing North Suburban Metropolitan Area. 15 minutes from loop and large educational center. New clinic. New 150-bed hospital. Salary open, fringe benefits. Fridley Medical Center, P.A., 203 Mississippi Street, Minneapolis, Minnesota 560-2950.

WANTED: Young internist and pediatrician, board certified or eligible, to join 6-man group consisting of 4 GP's, a general surgeon, and a radiologist. College town of 5,500 only 30 miles from Twin Cities. Salary open with early partnership opportunity. Write or call collect: Ed Jenkins, Mgr., River Falls Medical Clinic, River Falls, Wisc., phone 425-5322.

WANTED CAMP PHYSICIAN: — Have openings in months of June, July and August for Doctor at Saint Paul area Boy Scout Camp, Tomahawk, near Rice Lake, Wisconsin. Excellent facilities for doctor and his family for economical one to two weeks vacation. Contact D. E. Guenther, M.D., 1246 Gorman Ave., West St. Paul, Minn. 55118 or phone: 224-7581.

Continued

GENERAL PRACTITIONER — Well established 14 man multi-specialty group (seven general practitioners) midwestern city, population 30,000. Beginning salary, then partnership; no investment. Clinic building six years' old; excellent school, hospital and recreational facilities. Write: MINNESOTA MEDICINE — 343, 496 Lowry Medical Arts Building, St. Paul 55102.

GENERAL PRACTITIONER — to join established five-man mixed group in progressive city of 15,000 in Southeastern Minnesota. Excellent clinic facilities situated adjacent to hospital. Annual vacation, post-graduate time, retirement and other benefits. Starting salary open with eventual equal salary and ownership. Contact: Richard F. Lehigh, Owatonna Clinic, 134 Southview, Owatonna, Minnesota.

OPENING FOR PHYSICIAN in clinic; general practice; city of 2,000 in northern Minnesota; new 40-bed hospital. Warren Clinic, Warren, Minnesota 56762.

CLINIC LOCATION across from Knollwood and Target Stores. Ample ground and parking space. Will build and lease for interested group, or sell. J. Russell Carroll, 17 Tenth Avenue South, Hopkins, Minnesota. 935-4468.

GENERAL PRACTITIONER, associate, urgently needed. Unopposed practice established 20 years. 32 bed new hospital with additional 20 bed chronic unit. Good anesthesia coverage, lab. facilities. Excellent clinic one block from hospital. Salary with early partnership. Locum tenens also considered. Call collect 218-782-4725 or write Klefstad Clinic, Greenbush, Minnesota.

EXCELLENT DOCTORS' CLINIC available Crystal area — parking and air conditioned — 1500 square feet — will make special rental concession to doctor or doctors interested. Call S. J. Fischman TA 3-3556 or WA 6-2929 in Minneapolis.

OTOLARYNGOLOGIST TO join long established group with possibility of partnership in mid-west area. All instrumentation for entire ear, nose and throat available including the operating microscope. Write: MINNESOTA MEDICINE — 339, 496 Lowry Medical Arts Building, St. Paul 55102.

INTERNIST. Attractive position with six man medical group in northeastern Minnesota. Well equipped thirty-eight bed accredited hospital and two large hospitals in community twenty miles away. Work as consultant on clinic and hospital medical problems. Ideal for physician desiring a small community practice. No investment; full partnership after six months. Contact Community Clinic, Two Harbors, Minnesota.

SOUTH MINNEAPOLIS-RICHFIELD-BLOOMINGTON. 2 choice locations for proven office space near Hub Shopping Center. 11 doctors and dentists now operating in one location and 9 doctors and dentists in other building. Have space available for 1 dentist and 3 doctors. Contact Don Balmer, 2401 W. 66th Street, Richfield, Minnesota. Un. 9-3241 or Un. 9-4059.

GENERAL PRACTITIONER to join general practitioner affiliated with group in neighboring town in northeastern Minnesota. Basically medicine and pediatrics on outpatient basis. Obstetrical and hospital practice optional. Eight days off each month in any mutually agreeable manner plus liberal vacation and study leave. No investment; full partnership after six months. Present doctor spends time in medical missionary work. Age no barrier. Contact Community Clinic, Two Harbors, Minnesota.

WANTED — General practitioner to join a busy 3-man group and fill a vacancy left by retirement. Excellent salary first year, followed by full partnership. This progressive central Minnesota town of 2,000 has excellent hospital and clinic facilities, and is in a good farming area containing many lakes. Write: Paynesville Clinic, Paynesville, Minnesota.

THREE MAN Minneapolis GP group desires M.D. with Minnesota license to work during all or some parts of the spring and summer months. Salary open JA 9-9251.

BUSY, GROWING aggressive 3-man partnership in Northwest Wisconsin serving a trade area of 15,000 needs a well-trained recent graduate with fulfilled military obligations to associate immediately on excellent salary, with partnership in 1 year if mutually agreeable. Modern 15 room air conditioned brick clinic building is being doubled in size this year. 32 bed hospital and new 42 bed nursing home one minute from clinic. New 1500 student consolidate school. Excellent hunting, fishing and outdoor sport facilities in immediate area. Contact: MINNESOTA MEDICINE — 317; 496 Lowry Medical Arts Building, St. Paul 55102.

WANTED: Young MD with interest in pediatrics to join established four-man clinic group in Minnesota. Modern clinic building. Members in thirty-six to forty-eight age group. Surgery — OB GYN — Internal Medicine — EENT covered. County seat. Modern hospital. Good hunting and fishing. Excellent eighteen-hole golf course. Progressive farming. Vacation area. Salary open — leading to partnership. Contact: Business Manager, Lake Region Clinic, 1135 Washington Ave., Detroit Lakes, Minnesota.

WANTED: OB-Gyn in well established group in city of 15,000. Good hunting and fishing, we have over 1,000 lakes in county. Excellent hospital and clinic facilities. Write: V. I. Hanson, Business Manager, Park Region Medical Center, Fergus Falls, Minnesota.

RESIDENTS IN PSYCHIATRY — Opening for July 1st 1966 and January 1st 1967. Stipend $11,400 for physicians just completing internship. Federal stipend available to physicians with 4 years non-psychiatric training or experience following internship amounting to $12,000 annually with an extra $3600 tax exemption. Graduates of American Schools must be eligible for Iowa licensure. Foreign graduates must have ECFWG certificate. Hospital has 450 in-patients, large out-patient dept., children's unit with Board-certified Child Psychiatrist. Eclectic program with emphasis on community and existential psychiatry. Thirteen senior staff members including ten Board certified. Numerous consultants. Authorized for 12 residents. Affiliation with University of Iowa. Enthusiastic and dynamic training and treatment programs that are best understood by a personal visit. Write or call collect: W. C. Brinegar, M.D., Superintendent or John Worthington, M.D., Mental Health Institute, Cherokee, Iowa.

Classified Advertising

WANTED TEMPORARY older nurse-technician for small office. Write: MINNESOTA MEDICINE — 353, 496 Lowry Medical Arts Building, St. Paul 55102

CONTINUALLY GROWING AGGRESSIVE five-man established medical corporation in need of an additional general practitioner. In the group at the present time are three active general practitioners, a board-certified surgeon — well trained, and a board eligible obstetrician and gynecologist. This group is in the northwestern suburban area of Minneapolis with all the financial benefits of an established medical corporation. There is a new 150-bed hospital within five minutes from the clinic office. Please send letter to: Dr. A. H. Mork, Mork Clinic, Anoka, Minnesota if interested in further information.

PART TIME FILL-IN LICENSED DOCTOR for emergency room, Mondays and Fridays, 8 a.m. to 5 p.m. Contact: Mr. Stephen Sprint, Personnel Director, St. Joseph's Hospital, St. Paul 222-2861.

A THREE MAN GROUP needs a fourth general practitioner in a fast-growing West St. Paul area. Begin with salary and join partnership with full participating advantages. Write: MINNESOTA MEDICINE — 305, 496 Lowry Medical Arts Building, St. Paul 55102.

WANTED AT ONCE — a general practitioner — present physician retiring after 29 years. Opportunity to take over established practice with no obligation. Office space for rent and equipment available. New and accredited community hospital. Full details upon request. Write: Albert J. Emond, M.D., 720 Third Street, Farmington.

OFFICE FOR RENT. Occupied by doctors for 40 years. Almost completely furnished. Corner State and Concord Streets, Rent $75.00 month. Contact: M. D. Hunsbaker, 176 Concord Street, St. Paul.

PHYSICIAN AVAILABLE. Board surgeon with background general practice and surgery wishes to locate in Twin Cities area. Will also consider locum tenens. Write: MINNESOTA MEDICINE — 352, 496 Lowry Medical Arts Building, St. Paul 55102.

EASTERN WISCONSIN CLINIC in rapidly growing community of 40,000 desires board-eligible or certified physicians in pediatrics, obstetrics and gynecology and internal medicine. Well-equipped clinic and excellent hospital facilities. Lakeshore location offers ample recreational facilities. Attractive financial plan leading to early full partnership. Full expenses paid for applicants invited to interview. Call or write: F. L. Hildebrand, M.D., Riverside Clinic, Menasha, Wisconsin.

AVAILABLE FOR LOCUM TENENS the first three weeks in July. Contact: Dale T. Peterson, M.D., 946 F. Homestead Village, Rochester, Minnesota 55901 288-3432.

GENERAL SURGEON — board certified — 32 — university trained — numerous publications — military completed — one year of surgical practice — desires association or group practice. Cuniculum vitae available. Write: MINNESOTA MEDICINE — 354; 496 Lowry Medical Arts Building 55102.

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Contraindications: In hyperexcitability and in agitated prepsychotic states. Previous allergic or idiosyncratic reactions.

Precautions: Use with caution in patients hypersensitive to sympathomimetic compounds, who have coronary or cardiovascular disease, or are severely hypertensive.

Dextro-amphetamine sulfate: Use by unstable individuals may result in psychological dependence.

Meprobamate: Careful supervision of dose and amounts prescribed is advised; especially for patients with known propensity for taking excessive quantities of drugs. Excessive and prolonged use in susceptible persons, e.g. alcoholics, former addicts, and other severe psychoneurotics, has been reported to result in dependence. Where excessive dosage has continued for weeks or months, reduce dosage gradually. Sudden withdrawal may precipitate recurrence of pre-existing symptoms such as anxiety, anorexia, or insomnia; or withdrawal reactions such as vomiting, ataxia, tremors, muscle twitching and, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, reduce dose—operation of motor vehicles, machinery or other activity requiring alertness should be avoided. Effects of excessive alcohol consumption may be increased by meprobamate. Appropriate caution is recommended with patients prone to excessive drinking. In patients prone to both petit and grand mal epilepsy meprobamate may precipitate grand mal attacks. Prescribe cautiously and in small quantities to patients with suicidal tendencies.

Side Effects: Overstimulation of the central nervous system, jitteriness and insomnia or drowsiness.

Dextro-amphetamine sulfate: Insomnia, excitability, and increased motor activity are common and ordinarily mild side effects. Confusion, anxiety, aggressiveness, increased libido, and hallucinations have also been observed, especially in mentally ill patients. Rebound fatigue and depression may follow central stimulation. Other effects may include dry mouth, anorexia, nausea, vomiting, diarrhea, and increased cardiovascular reactivity.

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Minnesota Medicine at a Glance

Immunogenesis — Good et al. Page 725

In experimental medicine the "central lymphoid tissues" offer an exciting role in both normal and abnormal immune responses in their contribution to lymphomagenesis. The manuscript of Good et al. will be worth a careful study in order to keep abreast of this new development.

Human Serum Cholesterol Synthesis — Taylor et al. Page 728

The mysteries of cholesterol metabolism can be traced by using heavy water (D_2O). Eight serum cholesterol synthesis studies were carried out on five healthy human subjects — alternating them between cholesterol-rich and cholesterol-poor diets and monitoring the cholesterol response. The studies indicate that man, unlike the dog and cat, has no "feed-back" mechanism to compensate for changes in his diet cholesterol. Endogenous cholesterol is apparently delivered to the plasma at an unaltered rate regardless of diet. Physicians caught up in the continuing cholesterol controversy will find this article absorbing.

Hyperparathyroidism and Hypercalcemic Crises — Flink et al. Page 734

Hyperparathyroidism masquerading as a variety of diseases can produce acute and sometimes fatal illness. The clinical evaluation and laboratory tests are significant in making an accurate diagnosis. In any individual in whom there is profound muscular weakness and progressive hypotension there is usually associated nausea, vomiting, weight loss, lethargy, confusion, abdominal pain, polyuria, polydipsia, and constipation, with the emphasis resting on muscular, gastrointestinal, and mental symptoms which have a tendency to occur in a hypercalcemic crisis.

Four cases of this dramatic disease have been described by Flink et al.

Lung Function — Ebert Page 745

In pulmonary emphysema there is destruction of the normal architecture of the lung, alveolar septa are lost, and the normal air spaces are replaced by larger air-containing structures of variable size. This results in diminution of the diffusing capacity and the surface area to which blood and oxygen can be exposed. Resistance to air flow which is dependent on the velocity at which the air passes over the available space, and bronchial obstruction which is in turn dependent upon the pressure between the alveoli and and the lumen of the bronchus can also contribute to pulmonary incapacity. Any disease which modifies the magnitude of these structures will result in malfunction of the lungs.

Macroglobulins — Bell and Neumann Page 753

Bell and Neumann review their experiences with eight cases of macroglobulinemia. To detect the presence of macroglobulins they used paper and starch gel electrophoresis, the Sia test, dissociation of globulins with penicillamine, and ultracentrifugation. Seven patients had varying combinations of liver, spleen, and lymph node enlargement. One was referred with a diagnosis of lupus erythymatosus. All demonstrated excessive lymphocytes or atypical mononuclear cells in their marrow, and all had elevated sedimentation rates. The authors conclude that the most reliable tests are paper electrophoresis, immunoelectrophoresis with gamma IM antiserum, penicillamine disassociation, and ultracentrifugation.

Transfusions in Auto-Immune Hemolytic Anemia
— Yunis and Bridges Page 759

In auto-immune hemolytic anemia it is frequently difficult to obtain a perfect crossmatch. Additional laboratory studies must be carried out to find the least incompatible blood for transfusion.

Yunis and Bridges collect 40 patients with auto-immune hemolytic anemia. They describe their techniques in searching for etiologies. This manuscript gives a compact description of a technically baffling problem.

Sequelae of Prematurity — Branthaver Page 803

The sequelae of prematurity are often not observed until the child begins to function and associate more extensively with her peers. The only finding in this six-year-old girl was that of spasticity of the lower extremities which did not interfere with her ambulation except to give her a clumsy gait. In evaluating this girl's various skills it was found that she was slightly below average in some phases but a bit above average in others. She found it difficult to follow directions for abstract tasks, and she was considered to be in the low educable mentally retarded range.

After studying this child in conference, it was decided that management of her educational program would rest with the school authorities in cooperation with the mother.

Gastrointestinal Scleroderma — Grand Rounds Page 827

Previously, scleroderma has been considered to be primarily a dermatologic disease, but in recent years systemic manifestations, principally in areas of the gastrointestinal tract, have become evident. Dermatologic manifestations are not always evident, but when progressive dysphasia and articular pains develop, one should be suspicious of this condition. A variety of treatments have been found to provide partial relief.

Normal Values — Alexander Page 851

The normal ranges for most laboratory values are based on different samples of the populations and vary from hospital to hospital and from textbook to textbook. The clinician may find himself faced with a dilemma when he is presented with a normal value. This paper shows why normal isn't necessarily normal.

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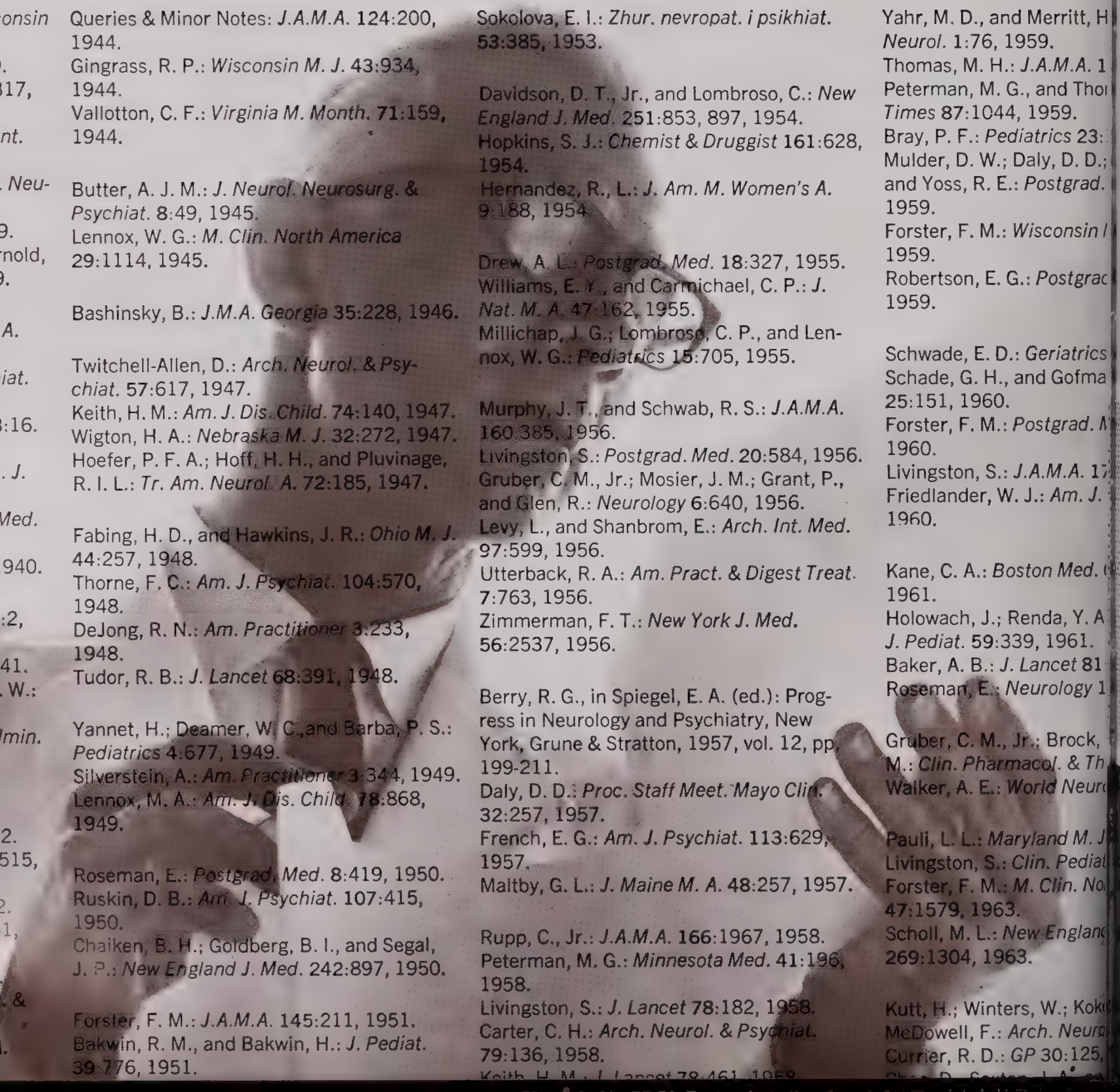

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Anatomy of
Low Back Pain #1
the sedentary life
is often the seat of
low back pain

The human spine is not engineered for prolonged sitting at desks, pianos, typewriters and drafting boards. The stresses set up by the heavy, forward-tilted head and trunk, balanced precariously on an insufficient base, result in strain of the dorsal musculature, particularly at the low lumbar level.

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President's Letter

"You may be right" and no buts will be added.

Several letters, and quite a few conversations, make it obvious that there are a number of physicians sincerely opposed to some Association policies, and concerned that no avenue of communication is open between them and Association membership.

It has never been Association practice to mute any voice of dissent, but it may be that the usual avenues, Reference Committee attendance, House of Delegate participation, or appearance before the Council are too technical, too formal, or inappropriate in time.

Consequently, after discussion with Dr. Carl O. Rice, Editor, MINNESOTA MEDICINE is introducing a new section, experimental in a sense, provocative in approach, and directed to what appears to be a need; a forum for member expression in print.

It is well to note the challenge in the title of this new section — "You May Be Right" — a challenge to consider, to weigh, and to be factually sure before committing any opinion to the judgement of the readers.

Now that motherhood is losing to the expanding claims of competing pill makers, and sin, not adopting new faces, is only exposing old breasts, areas of previous total agreement are obviously decreasing. But following Federal intervention in patient care in a manner never dreamed of by the Congress which made the act a law, many new situations creating strong, and strongly diverse, opinions are developing.

Certainly, any statement of Association policy must represent the consensus, but it seems logical that some opportunity should be provided for the minority who disagree, and want to explain the basis for that disagreement.

The potentials of this new venture are as wide as medical interests, are not restricted to any area, and have no boundaries other than reader interest and good judgement on the contributors part.

The use of space, and the determination of reader appeal are a matter of editorial judgement. Editing, condensing and possible rejection will be, as always, editorial prerogatives. Familiarity with the high standards of MINNESOTA MEDICINE is, however, an assurance that the same standards will apply to this new venture.

R P Buckley M.D.

R. P. Buckley, M.D.
President
Minnesota State Medical Association

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be a bitter pill
to swallow?

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Primary Aldosteronism

GEORGE M. B. HAWLEY, M.D.
Red Wing, Minnesota
LOUIS TOBIAN JR., M.D.*
Minneapolis, Minnesota

IN JULY OF 1962 there were 205 published or well documented cases of primary aldosteronism. Since that time there has been a great increase in the rate of detection of this syndrome throughout the world, and it is estimated that the number of established diagnoses is now many hundreds.[1] This communication reports the unmasking of the clinical features of this condition by the administration of a thiazide diuretic. It also deals with the problem of residual hypertension after an aldosteronoma has been removed.

Case Report

The patient was a 46-year-old single white female with a background of general good health aside from symptoms of nervousness and anxiety. Her 80-year-old mother had essential hypertension. On a routine physical examination in 1949, at age 32, the patient's blood pressure was 140/88. Facial acne and a seborrheic dermatitis of the trunk were noted. An excess of coarse black hair was present on the forearms and legs and there was a male escutcheon. The urine specific gravity was 1.026 and the pH 8.0. At age 37 her blood pressure was 156/94; at age 44 it was 210/108. She was not seen again until age 45 (1962). On six occasions during a subsequent eight-month period, her blood pressures varied from 212/106 to 224/120. On two occasions she was placed on a reserpine-thiazide preparation for one month, with no significant symptomatic response or change in her blood pressure levels. On 10-27-62, because of the hypertension, hirsutism, and facial acne, she was referred by her gynecologist to one of us to rule out the possibility of Cushing's syndrome. Her urine 17 ketosteroid and 17 hydroxycorticosteroid levels were normal. She was given a preparation containing 4 mgm. of trichlormethiazide and 1/10 mgm. of reserpine to be taken twice daily. Seven days later she noted the onset of progressive and pronounced weakness in both lower extremities, so severe that she fell to the floor when she attempted to stand. There was associated severe aching in the legs and intermittent paresthesias in both hands. On physical examination her blood pressure was 214/112. Generalized deep tendon hyporeflexia was present. At this time the possibility of a diagnosis of primary aldosteronism was considered. Her antihypertensive medication was discontinued and she was placed on supplemental potassium with prompt symptomatic and objective improvement. Ten days later, while still on supplemental potassium, her serum potassium level was 2.6 mEq/L., the serum chloride 97 mEq/L, and the sodium 143 mEq/L. Repeated urine examinations revealed a persistent alkalinity. Her kidneys were unable to concentrate the urine above a specific gravity of 1.015. She recalled that in recent months she had noted a moderate nocturnal polyuria. Two urine aldosterone determinations were reported as 35 mcg.% and 39 mcg.% (normal 3-32 mcg.%).

Laboratory Studies

The patient was referred to the service of one of us at the University of Minnesota Hospitals for confirmation of the presumptive diagnosis of primary aldosteronism. Further laboratory determinations at that hospital revealed the following values: blood urea nitrogen 8 mg.%, blood creatinine 0.8 mg.%, standard creatinine clearance 151/L in 24 hours, bicarbonate 36 mEq/L, chloride 97 mEq/L, sodium 144 mEq/L, and potassium 2.5 mEq/L. Serial daily potassium levels were in the range of 2.1 to 2.5 mEq/L. A blood volume determination done by the radioactive iodinated albumin technique was 5.9 liters. A chest film, electrocardiogram, and intravenous pyelogram were all within normal limits. A urine culture was sterile. Bilateral ureteral catherizations were performed to carry out a Rappaport test. This was considered to be normal and there was no evidence of renal arterial constriction. The serum calcium was 8.7 mg.% and the serum phosphorus 2.8 mg.%.

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*Professor of Internal Medicine, University of Minnesota School of Medicine.

A glucose tolerance test was interpreted as borderline diabetic. Two urinary 17 hydroxycorticosteroid levels were within normal limits.

The patient was started on large doses of supplemental potassium, up to 16 gm./day, and at the end of a week her serum potassium had risen from 2.8 to 5.1 mEq/L with a drop in bicarbonate to 23 mEq/L, and the appearance of an acid pH of the urine.

Operative Findings

On 12-10-63, using an anterior bilateral subcostal approach, the right adrenal gland was carefully dissected free and found to be normal to palpation by Dr. Richard L. Varco, Department of Surgery, University of Minnesota School of Medicine. A tumor 1.2 cm. in all diameters was located in the left adrenal, and a total left adrenalectomy was performed. The patient had a postoperative diuresis of 3,000 cc. on the first postoperative day, with volumes during the next seven days ranging between 2700 cc. and 3500 cc. Nine days postoperatively her serum potassium was 4.2 mEq/L, serum sodium 137 mEq/L, and bicarbonate level 26 mEq/L.

Pathologic Findings

The pathologist's examination of the excised nodule describes "a sharply circumscribed encapsulated round nodule composed of cords and columns and nests of rather large cells arranged in a rooftile pattern, these cells having abundant, mostly clear, somewhat granulated cytoplasm, and round, small, nuclei with a distinct fine chromatin network. There is some variation in nuclear size and outline. The cells are subdivided into small lobules by very delicate connective tissue septa containing small and large blood channels. The appearance is that of a cortical adenoma of the adrenal gland and presents no features which might indicate its metabolic activity" (Figures 1 and 2).

Postoperative Course

The patient returned to her home two weeks after surgery but was hospitalized two days later because of the development of a hematoma in her right thigh. During the following eight days her blood pressure ranged from 136/74 to 160/110. She had lost 18½ lbs. in her immediate postoperative period and now weighed 123 lbs. On 1-8-64 her blood pressure was 162/106. The urine pH was 4.5 with a specific gravity of 1.018. On 2-3-64 the blood pressure was 186/120, and eight subsequent readings taken at intervals of one month ranged from 168/102 to 196/110. A urine concentration determination on 6-15-64 revealed a maximum specific gravity of 1.021 and her serum potassium was 5.1 mEq/L. On 9-22-64 she was placed on 1.5 gm. of chlorothiazide* daily and continued on a low sodium diet. Her serum potassium one week later was 3.7 mEq/L. On 9-29-64 her dosage of chlorothiazide was increased to 2 gm. per day. Her serum potassium on 10-17-64 was 4.0 mEq/L. Subsequent blood pressure readings at intervals of one month ranged from 148/98 to 160/100 mm. of mercury. On 5-20-65 the patient was asymptomatic and her urine pH was 5.0 with a specific gravity of 1.019. The 8:00 a.m. plasma cortisol level was 16 mcg.% and the 8:00 p.m. specimen less than 5 mcg.%. The BUN was 18 mgm.%, creatinine 1.3 mgm.%, uric acid 8.0 mgm.%, bicarbonate 30, chloride 99, sodium 137, and potassium 3.7 mEq/L. It was felt that the modest hypokalemia and hyperuricemia were probably due to the use of chlorothiazide to control her hypertension.

Discussion

The symptoms and signs of primary aldosteronism have been clearly defined and are attributable to (1) potassium depletion, (2) hypertension, and (3) hyposthenuria. The clinical manifestations are usually vague and seldom clear-cut unless accelerated potassium depletion is effected by diminished intake, gastrointestinal losses, or as in our case, increased renal loss after the administration of a thiazide diuretic. In the patient presented here, the thiazide acted as a provocative test for primary hyperaldosteronism. This may prove to be a useful procedure in other suspected cases. Metabolic alkalosis is usually present along with elevated values of aldosterone secretion.

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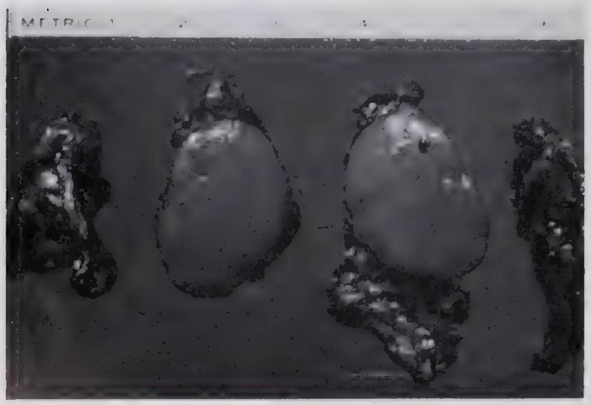

Fig. 1 — Surgically excised adrenal tissue showing the aldosterone-secreting adenoma.

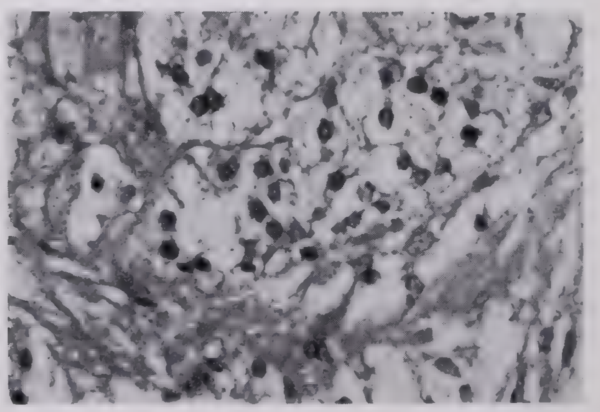

Fig. 2 — Photomicrograph of aldosterone-secreting adenoma.

Before adrenalectomy is performed, hyperaldosteronism secondary to renal vascular hypertension, malignant hypertension, nephrosis, cirrhosis, and cardiac insufficiency should be carefully considered. In most hypertensive patients with secondary aldosteronism the serum sodium is either normal or low, and alkalosis, if present, is usually mild. In hypertension with secondary aldosteronism, the serum potassium level is usually between 3 and 4 mEq/L. In the hypertension of primary aldosteronism, the serum potassium is usually below 3 mEq/L. Conn[2] states that in primary aldosteronism the secretion of renin is severely depressed, whereas in aldosteronism secondary to renal vascular disease renin activity is increased. He feels that eventually renin levels will be used effectively to differentiate these two conditions.

The extreme importance of effecting potassium balance prior to adrenalectomy has been emphasized by Zimmerman and others.[3] A case has been reported where over a period of eight years potassium supplements of 8-12 gm. daily were able to maintain normal serum potassium levels and the patient in a symptom-free state.[4]

After the removal of the adenoma in our patient, the tendency to severe hypokalemia disappeared even when large doses of thiazide were given. Moreover, the pH of the urine ceased to be continuously alkaline, and the ability to form a concentrated urine was restored. The level of arterial pressure was also reduced but still remained in the hypertensive range. This residual hypertension can be accounted for either by an underlying essential hypertension which preceded the aldosteronoma or by the appearance of "metacorticoid" hypertension, or by both. The term, "metacorticoid hypertension" is used to describe a hypertensive syndrome in rats. If a rat receives desoxycorticosterone and salt for only six weeks and becomes hypertensive, removal of the desoxycorticosterone and salt usually allows the blood pressure to return to normal. However, if the desoxycorticosterone and salt are administered for as long as five months, the hypertension may persist indefinitely even after the desoxycorticosterone and salt regimen has been discontinued.

The hypertension which results in man from an aldosterone-secreting adenoma resembles desoxycorticosterone hypertension in the rat. Therefore, the residual hypertension which is present following removal of an aldosteronoma may be the human counterpart of "metacorticoid" hypertension in the rat.

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An Overestimate?

There are men and classes of men that stand above the common herd; the soldier, the sailor, and the shepherd not infrequently: the artist rarely; rarelier still, the clergyman; the physician almost as a rule. He is the flower (such as it is) of our civilization. . . . Generosity he has, such as is possible only to those who practise an art, never to those who drive a trade; discretion, tested by a hundred secrets; tact, tried in a thousand embarrassments; and what are more important, Herculean cheerfulness and courage. — Robert Louis Stevenson (1850-1894)

Prejudice

Prejudice is being positive about something negative. — Phoenix Flame

Congenital Hip Subluxation

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RICHARD CUSHING, M.D.[**]
ARNOLD S. ANDERSON, M.D.[**]
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THE DIAGNOSIS of congenital hip dysplasia in the first six months of life leads to effective and successful management of this difficult problem. Early diagnosis is possible only if the initial findings are clearly understood by the examining physicians of the newborn child and if follow-up is maintained throughout the first twelve months of post-natal care.

The published works of Vernon Hart,[9] H. R. McCarroll,[13] and L. E. Harris et al.[8] provide an excellent criterion for the early diagnosis of congenital hip dysplasia. Recent studies[1,2,4,22] have shown that the primary anatomical defect is in the laxity of the capsule. This laxity may be due to hormonal factors, which subsequently develop into either congenital subluxation or dislocation of the femoral head. The generally accepted theory that inadequate acetabulum is the primary cause has been found to be incorrect by arthrogram studies, as pointed out by Mitchell[14] and Somerville.[19,20] We[11] have verified the Somerville findings through our own arthrogram study and by dissection of acetabula in fetuses of many ages. Evidence tends to show that shallow acetabulum and excessive femoral anteversion are the results of subluxation or dislocation.

Hip dysplasia is divided into two categories, *subluxation* and *dislocation.* Subluxation is defined as upward or lateral displacement of the femoral head, where motion still occurs between the femoral head and the acetabulum. Complete dislocation is a type of hip dysplasia in which the femoral head is completely out of the acetabulum. According to Somerville, in subluxation the acetabulum is still the fulcrum around which movement takes place; but in a dislocation, it is not.

In the newborn child, the most reliable guide or sign of hip dysplasia is *limitation of abduction.* It is not unusual to find a limitation of 30 degrees up to the age of six months in normal hips. However, if the limitation of abduction exceeds 30 degrees or

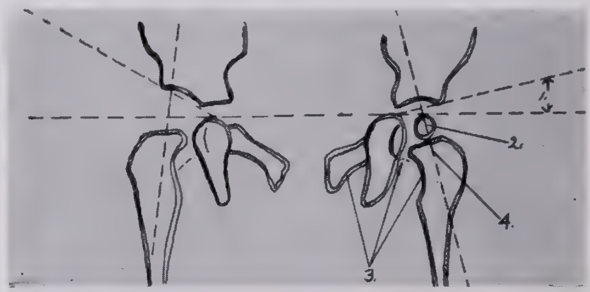

Fig. 1 — Diagrammatic representation of the roentgenographic criteria in congenital hip dysplasia noted in anteroposterior projection.

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[*] This study is supported by a grant from the St. Louis Park Medical Center Research Foundation.

[**] St. Louis Park Medical Center, Minneapolis, Minnesota.

Requests for reprints should be addressed to the St. Louis Park Medical Center, 4959 Excelsior Blvd., Minneapolis, Minnesota.

and Dislocation in Early Infancy*

Management
of

more to assume complete abduction of 90 degrees, the finding warrants roentgenographic examination. Inequality of leg length, abnormal thigh and gluteal creases are inconstant findings in subluxation; in complete dislocation, limitation of abduction, shortening of the affected leg, and positive Ortolani[15] click are diagnostic findings. It is not unusual to have full abduction in complete dislocation, as the femoral head is either completely free of the joint or is relocated in the process of abduction. Anteroposterior projection, frog-leg position, and, sometimes, the Van Rosen[15,16] view, if necessary, usually confirm the diagnosis. The Van Rosen view is an anteroposterior projection taken with the hip in at least 45 degrees of abduction and 15-30 degrees of internal rotation. It is important to note that one must not relocate the femoral head during the process of abduction and internal rotation. If on this view the axis of the femoral neck is found to point to the anterosuperior iliac spine, or superior to it, the femoral head is dislocated.

This study is an analysis of 103 patients, 85 females and 18 males, treated at the St. Louis Park Medical Center, Minneapolis, Minnesota, in a twelve-year period (1952-1964). The current study of all the charts and x-rays available produced data on 84 subluxations and 19 dislocations. Of the 84 subluxations, 82 cases or 97 per cent were diagnosed below six months of age; 61 patients or 73 per cent were diagnosed in the first three months of age. In congenital dis-

TABLE 1

Congenital Hip Subluxation and Dislocation
103 Cases (1952-1964)

Diagnosis:	84 Subluxation 19 Dislocation
Sex:	85 Female 18 Male
Ratio:	5:1

TABLE 2

Age at Diagnosis
102 Cases

Subluxation:	82 or 97% Less Than Six Months of Age 61 or 73% Less Than Three Months of Age
Dislocation:	3.9 Months Average Age (2-6 Months) Cases Primarily Seen at SLPMC Since Birth 15 Cases or 78.0%
	11.2 Months Average Age (9-15 Months) Cases Referred to SLPMC 4 Cases or 23%

location, the average age of diagnosis was found to be seven months. In 15 infants who were primarily seen at the St. Louis Park Medical Center since birth, the average age of diagnosis was 3.9 months (Table 1 and 2).

Diagnostic Signs

Abduction Test

The abduction test is the most reliable examination for detecting hip dysplasia in the newborn child (Table 3).[8] This test is done by laying the infant flat on his or her back on a firm examining table. With the thigh and knees flexed at 90 degrees, the hips are abducted. Ninety-six out of the 103 patients were found to have limited abduction. Three patients with dislocation had normal abduction. The other four had shortening of one leg, abnormal thigh creases and normal abduction.

Ortolani Click

Ortolani and Barlow described the click as a pathognomonic sign of congenital dislocation of the hip in infants from birth to a year old. In this test the child is laid on his back with hips flexed at right angles and knees flexed. Then the hips are slowly abducted, and somewhere in the 90-degree arc of abduction, a click is elicited as the femoral head slips back into the acetabulum. In our study, 68 per cent of the 19 dislocations had a positive click; only three cases of subluxation were found with a positive Ortolani sign. The x-rays of the latter patients indicated subluxation rather than dislocation.

TABLE 3

Incidence of Limited Abduction, Leg Shortening, Abnormal Crease and Ortolani Click in 103 Cases

Limited Abduction	96 or 95%
Leg Shortening (Allis Sign)	14 or 13%
Abnormal Gluteal or Thigh Creases	7 or 6.8%
Ortolani Click Dislocation	13 of 19 or 68%
Ortolani Click Subluxation	3 of 84 or 2%

TABLE 4

Follow-up and Results

Follow-up	Subluxation	70 Patients, 12-84 Months 10 Patients, Less Than 1 Year 4 Patients Lost to Follow-up
	Dislocation	13 Patients, 18-72 Months (Average 35.8) 6 Patients, Less Than 18 Months
Results	Subluxation:	66 of 70 Patients - Normal Hips by Clinical Examination and Roentgenographic Criteria 4 Patients - Minimal Subluxation
	Dislocation:	12 of 13 Patients, Normal Hips 1 Patient, Minimal Subluxation

Shortening: The Allis Sign

Out of 103 cases 13 per cent were found to have a shortening of the affected limb. There were two cases of subluxation and 12 of dislocation. This test is done by laying the infant flat on his back with the knees and hips flexed 90 degrees. The sign is positive if the affected thigh is shorter than the opposite thigh. Comparing the level of the soles of the feet is fraught with errors, as the pelvis may be tilted from other causes or inadvertently tilted during the examination, thus giving a false positive sign.

Abnormal Crease

Only seven out of the 103 patients were found to have an abnormal crease either in the thigh or gluteal folds. The low incidence in this series probably results from the fact that the examining physician did not make a notation or did not pay particular attention to this sign.

Radiologic Diagnosis

Interpretation of x-rays is difficult in the first six months of age because of the absence of the femoral head. Ninety of the patients had x-rays available for study; in the remaining cases the diagnosis was taken from the radiologist's report. Four criteria were noted in the anteroposterior projection, as illustrated in Figure 1.

1. *Acetabular angle.* The acetabular angle was measured by the Hilgenreimer[10] method, before the onset of treatment, after treatment, and on the final follow-up x-rays.

2. *Presence or Absence of the Capital Epiphysis.* This is of little value in the first six months, because it is seldom evident at this time. However, in following a patient's case,

a delay in appearance compared to the normal side or inequality of size is considered corroborative evidence of congenital hip dysplasia.

3. *Shenton's Line.* In a normal hip, this is an arc formed by the inferomedial border of the neck of the femur and the superior border of the obturator foramen. A break in this line occurs when the femoral head or neck rides superiorly, laterally, or both, in relation to the acetabulum.

4. *Direction of the Central Axis of the Head and Neck or Femoral Neck in Relation to the Acetabulum.* No measurement was made in this method except by direct visualization.

There were 84 subluxations (two or more positive roentgenographic criteria) and 19 dislocations.

In the cases studied, the acetabular angle averaged 32 degrees (20 to 43) in the affected hip, while the normal hip averaged 23 degrees (12 to 31). Seventy-seven per cent of the cases were found to have increased acetabular angle, when compared to the normal hip. Caffey's[5] study shows a much greater variation in the acetabular angle in normal infants. The important thing to be noted, however, is the inequality of the acetabular angles in the same infant and its correlation with the clinical findings. The acetabular angle reflects only the osseous development of the acetabulum. Our arthrogram study and fetal dissections showed that the acetabulum covered the femoral head adequately in spite of an apparent shallow acetabulum in anteroposterior projection roentgenograms (Figures 2-a and 2-b).

Eighty-one per cent of the 103 cases had an abnormal Shenton's line.

Of the 84 subluxations, 24 per cent have been noted to have delayed, smaller, or absent capital epiphyses compared to the opposite normal hip on the initial x-rays. Of the congenital dislocations, 52 per cent have delayed or smaller capital epiphyses.

Eighty-nine per cent were found to have deviation of the central axis of the femoral head and/or neck from the center of the acetabulum.

Management

Hip Subluxation

For subluxations, an abduction pillow splint (a modified Frejka splint) made by the parents under the guidance of the pediatric nurse has been most successful. The average duration of treatment is 4.4 months, with a range of one to 15 months. This usually involves the continuous use of a pillow splint for three months, followed by one month in which it is applied only during the night and long napping times. Termination of the use of the splint is based upon both clinical and x-ray findings; the x-ray criteria

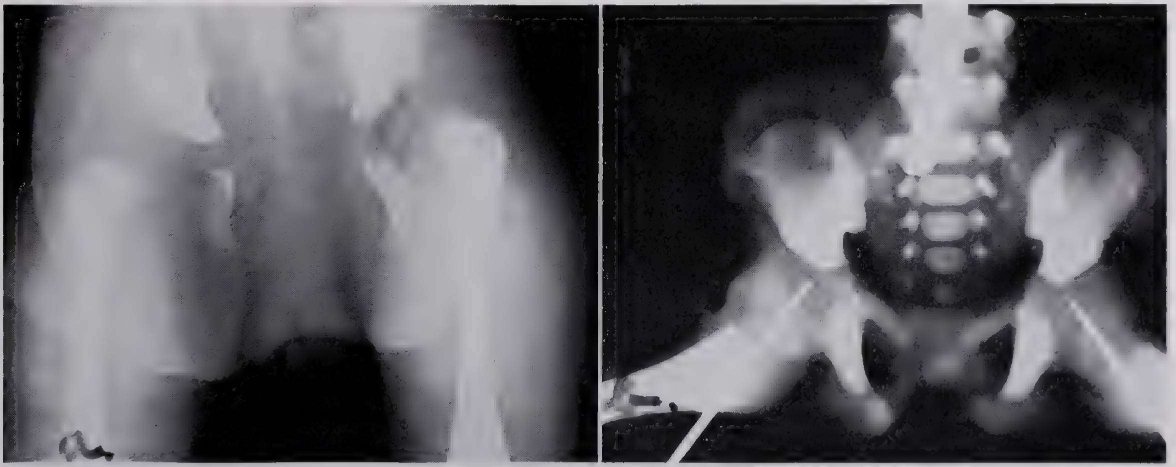

Fig. 2(a) — Anteroposterior roentgenogram of both hips of a dead fetus, showing complete dislocation of the left hip. The acetabular angle is markedly increased. (b) — Anteroposterior roentgenogram of both hips in the same fetus illustrates the vacuum phenomenon effect. There is a radiolucent area around the capital epiphyses and shows an excellent covering of the femoral head by the acetabulum.

are normal acetabular angles, central axis of the femoral head and neck well-centered in the acetabulum, and the capital epiphysis covered by at least three fourths of the acetabulum.

Congenital Dislocation

The treatment of congenital dislocation involves the following steps:

1. Preliminary traction for about 10 days to two weeks, unless the dislocation is noted in the first three months when the femoral head can be relocated easily. The traction is continued and maintained for several days, until the femoral head and neck are level with the inferior edge of the acetabulum.
2. Application of bilateral spica cast in frog-leg position. Adductor tenotomy should be done whenever the adductors are felt to be tight.
3. After three to four months in a bilateral spica cast, the infant is placed in a single spica cast in Lange's position for another eight to twelve weeks.
4. Upon removal of the cast, an abduction bar is applied with the hips at 45 degrees to each other and maintained for several weeks. The use of the abduction bar is then reduced to night-time application only and is finally discontinued when the hips appear normal by roentgenogram.
5. Derotation osteotomy may be necessary when femoral anteversion is excessive and persists.
6. These children should be followed for several years — at least until cessation of growth.

The average duration in a cast is seven months (3 to 18) and nine months in an abduction bar (3 to 24 months). Only one patient needed an open reduction to correct the dislocation; another required a derotation osteotomy to correct excessive anteversion of the femoral head and neck.

Arthrography

The arthrogram was employed in the last six congenital dislocations seen at the Medical Center to ascertain the accuracy of reduction and to determine the presence of intra-articular obstacles in the acetabulum. These are usually difficult to find on routine x-rays because of the absence of the femoral head. There are possible intra-articular obstacles, such as an hourglass labrum, a hypertrophied ligamentum teres, and an infolding of the capsule as reported by O. Scaglietti and B. Callandriello.[18] If such obstacles are present, preventing closed reduction of the dislocated hip, then open reduction and removal of the obstacle is advised. Thirty-three per cent Hypaque solution is used for arthrography; the amount usually required is 2 to 3 c.c. Interpretation requires experience and understanding of possible intra-articular obstacles to prevent false positive readings as shown in Figures 3-a and 3-b.

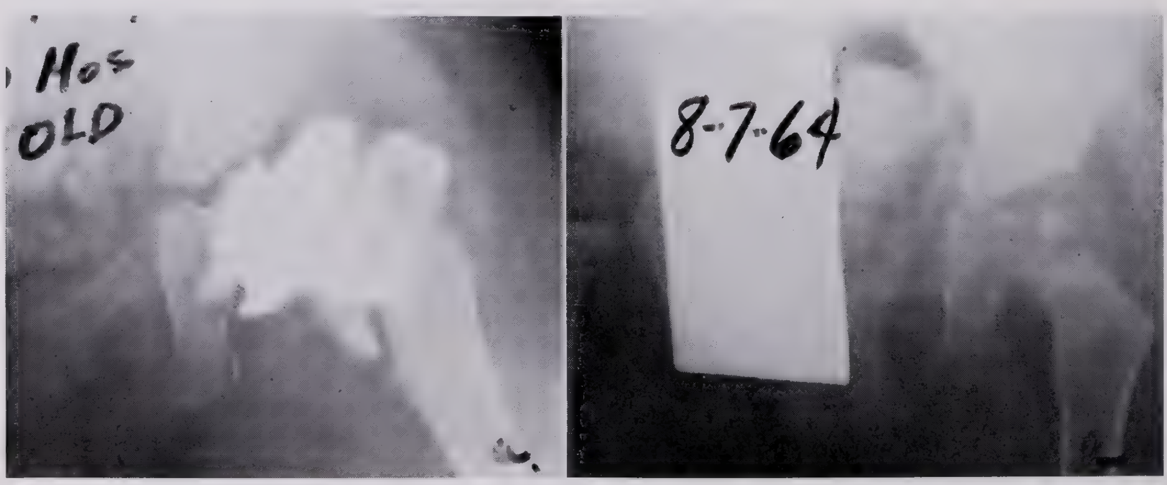

Fig. 3(a) — Arthrogram of the dislocated left hip in a 10-month-old girl showed a possible "hourglass defect" of the labrum or an infolding relaxed and redundant capsule. (b) — Five months later after closed reduction, AP roentgenogram showed the femoral head well seated in the acetabulum. The defect in the arthrogram represents an infolding capsule rather than a true hourglass labrum.

Results

Of the 84 subluxations, on the latest follow-up of 70 patients, 94 per cent have normal hips by roentgenogram. These patients were followed from twelve to eighty-four months after cessation of treatment. X-rays still indicate a minimal subluxation in four of the children after 12, 20, and 22 months of the follow-up. One patient developed a coxa vera, (Table 4).

Dislocation

Twelve out of 13 patients who had a dislocation have normal hips by x-rays and clinical examination after an average follow-up of 35.8 months (range of 18-72 months). One patient has a very minimal subluxation on x-ray, although clinically normal. This may be a case where early degenerative arthritis will develop. One child developed a valgus knee which is probably secondary to prolonged abduction bar, as this particular patient was in an abduction bar for fifteen months. To avoid this sequela, an abduction bar has been devised* which eliminates the valgus stress placed on the knee by the ordinary bar (Figure 4). Two years after treatment as has been outlined, one patient developed an aseptic necrosis of the femoral head in the same hip. This was difficult to differentiate from Legg-Perthes disease. The child was placed on an ischial weight-bearing brace until the capital epiphysis became fully revascularized.

Discussion

This study confirms the opening hypothesis that early diagnosis and adequate treatment is the key to an effective management of the congenital hip dysplasia. The real answer to the efficacy of our treatment, however, will be known forty to fifty years from now, when we can answer the question, "How many of these patients will develop degenerative arthritis secondary to a dysplastic hip?"

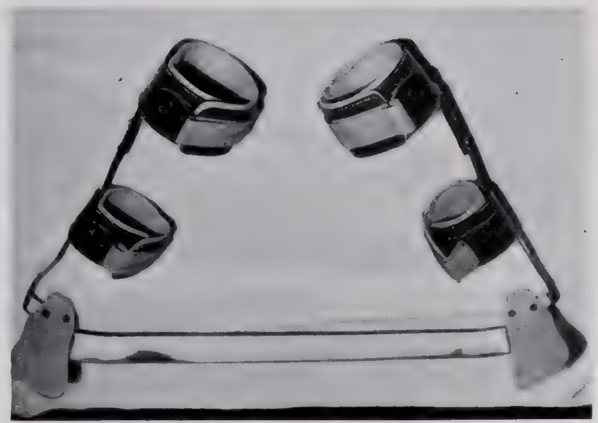
Fig. 4 — Indeck's Abduction Bar for congenital dislocation of the hip. This prevents valgus stress in the knee and allows the foot pieces to be turned in any rotation desired.

According to various studies, the casual relationship between osteoarthritis and hip dysplasia is alarmingly high, ranging from 20 to 48%.[7,12,21] For this reason, all subluxations, however minimal, and dislocations should be treated adequately until all criteria of a normal hip are attained. There are cases of spontaneous normalcy of a subluxed hip, but there is no way of telling which hip will become normal without treatment.

In cases of frank dislocation, the parents should be made aware at the start that treatment and care will be prolonged and will demand a great deal of patience on their part. These cases should be referred immediately to the care of an orthopedic surgeon.

From this study it is clear that a pillow splint, if properly applied and supervised, is an adequate treatment for congenital subluxation in early infancy. It must remain on until abduction is fully obtained and the roentgenographic features return to normal. Once the splint is applied, the child should be examined every six weeks to be sure that the splint is being used correctly. The second set of x-rays is not taken until three months after treatment. After correction is obtained in cases of subluxation, the patient should be followed for at least twelve months and, ideally, until cessation of growth. Not infrequently, we thought correction was obtained; then many months later signs of subluxation became evident again. In such a case one should not hesitate to start over with any treatment which may be necessary.

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*By Dr. Walter Indeck.

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2-22 May be secured from the author or the reprints.

Doctor, I've Got . . .

As I lay sleeping snug last night
A man appeared to me;
He said, "I suffer severe frost bite,
And chondromalacia, knee.

"Arteriosclerosis obliterans
Has luckily passed me by,
And my myositis ossificans
Would scarcely trouble a fly.

"But pruritus ani plagues me by day,
With superimposed erythema;
At night, wherever my legs I lay,
I'm troubled with pedal edema.

"Hypertension essential is what I've got,
And a mild cerebral thrombosis;
With partial aphasia, an aching gut,
And a scatter of keratosis.

"I've gout, neuritis, anxiety state,
And a touch of schizophrenia,
In remission, and complicated of late
By acute and pernicious anemia.

"Oh, I am an excellent candidate
For an early and careful trephining,
Or soon I'll be lying in lonely state
Where the gentle woodbine's twining."

I was wringing my hands for the wretched bloke
When he suddenly vanished in air;
And mercifully, I then awoke
From the night wind blowing my hair.

Else Sonne Nissen
Veterans Hospital
Iron Mountain, Michigan

There are many shining qualities in the mind of man; but none so useful as discretion . . . though a man has all other perfections and lacks discretion, he will be of no great consequence in the world; but if he has this single talent in perfection and but a common share of others, he may do what he pleases in his station of life. — Addison

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Doing an injury puts you below your enemy; revenging one makes you even with him; forgiving it sets you above him. — Nylic Review

Pseudomembranous Enterocolitis

A Comparison with Staphylococcal Colitis

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PSEUDOMEMBRANOUS ENTEROCOLITIS is a rapidly and highly lethal disease of unknown or variable etiology. Most of the literature credits Finney with the first description of this disease in 1893. However, Bloomfield[2] records a description by Bilroth in 1867.

Pathologic Characteristics

Mucosal necrosis is considered by Durrani[6] as an indispensable and outstanding morphologic feature. The necrosis is usually limited to the mucosa[11] and often involves only the tips of villi[19] or the mucosal folds.[11] Venules and capillaries, but never arterioles, are blocked by fibrinous thrombi.[11,19] The pseudomembrane resembles diphtheritic type and consists of necrotic mucous membrane, fibrin and inflammatory debris.[11,18,19] Kay[11] prefers to name this disease "acute necrotizing (pseudomembranous) enterocolitis." The distribution of the lesions classified from the largest series[20] involved small bowel in 44, small bowel and colon in 24, and colon alone in 12.

Clinical Features

Onset

Onset is sudden and is associated with shock and collapse.[6,8,14,20] In this respect it resembles the abrupt onset of Asiatic cholera.[5] Most of the larger series reported in the literature are from autopsy material.[2,4,6,14,19,20] Of 107 cases studied by Pettit,[20] only six lived 48 hours after shock was noted; 50 per cent died within 12 hours. Kay[11] found the same rapid deterioration in a 16-case study. Dixon[5] reported 91 per cent mortality in 23 cases. Frank peritonitis existed in 12 of the 21 deaths, and three showed a gangrenous segment of bowel. Pettit[20] found evidence of peritonitis in 63 per cent of his 107 autopsies. Eiseman[7] cited a 74 per cent mortality on the basis of three recently published reports.

Nearly all of the cases appear following surgery on the intestinal tract[5,18,19,20] and most commonly after a gastrectomy;[11] however, a few cases are described in the debilitated or chronically ill patient.[14] In one report[11] half of the nonoperated cases appeared in patients with cardiac problems. The interval between operation and onset of the pseudomembranous enterocolitis is very short, the highest frequency occurring the second or third day.[11,18,20]

Diarrhea

Though not a prominent feature, diarrhea,[5,6,11,20] when it does appear, is usually small in volume and of rice-water character.[5] Van Prohaska,[21] however, considers severe diarrhea to be an important sign. In view of the preponderance of opinion against this observation, it is quite likely that he is observing a different entity — namely, staphylococcic enteritis.

Causative Factors

Shock

Most authors[5,6,11,14,18] do not consider shock to be a causative factor, but rather a signal of the onset, i.e., a consequence of the disease. However, in the review of only one paper[19] is antecedent shock assigned an etiologic role in pseudomembranous enterocolitis by virtue of altered vasomotor mechanisms.

Impaired Circulation

Chronic arterial insufficiency is suggested as a predisposing condition, setting the stage for development of necrotizing lesions of the bowel mucosa. Marston[15] suggested that preexisting ischemia of the bowel of elderly persons sets the stage for the development of a group of obscure bowel lesions with necrosis, whenever a state of shock develops. Pseudomembranous enterocolitis, staphylococcic enteritis, infarction of bowel, acute necrotizing enterocolitis, and acute hemorrhagic necrosis of the gastrointestinal tract were all regarded by this author as variants of the same problem.

Wilson[27] considers acute hemorrhagic enterocolitis in the chronically ill to be due to chronic congestion and cellular anoxia of the bowel mucosa, and he further believes it to be a separate entity from pseudomembranous enterocolitis.

In the cases of mesenteric arterial obstruction reported by Shaw,[24] a malabsorption syndrome developed — possibly secondary to insufficient oxygen supply. The bowel, however, appeared to have no gross lesion.

Laufman[13] experimentally produced a gradual occlusion of mesenteric vessels in dogs; but in spite of this he observed only a low-grade enteritis and some small subserosal thrombi. The observations of Wilson,[27] Shaw[24] and Laufman[13] are, therefore, probably unrelated to pseudomembranous enterocolitis.

Antibiotics

The broad-spectrum antibiotics have been implicated by some authors[2,10,18,23,25] and absolved by others.[6,8,11,20] Johnston[10] considered a causal relation to exist, but all 14 of his cases recovered, casting doubt upon the accuracy of this classification. Valberg[25] found no staphylococci or other pathogens, even though all his cases had received antibiotics, and, therefore, postulated some direct deleterious effects of antibiotics on the mucous membrane. The most convincing evidence against the theory that antibiotics have a causative role is found in the Mayo Clinic Autopsy Series of 107 cases reported by Pettit,[20] who found an equal number of postoperative pseudomembranous enterocolitis cases in the pre and in the postantibiotic years.

Staphylococcus

Micrococcus pyogenes (staph) enterocolitis is known to produce a pseudomembrane as well as other features resembling pseudomembranous enterocolitis. However, considerable debate exists whether the conditions are the same or merely similar. The most convincing argument favoring staphylococcic etiology is presented in the study of van Prohaska and associates,[21,22,26] who believe that the remarkable response of pseudomembranous enterocolitis to corticotropin and erythromycin is evidence that staphylococcus enterotoxin causes the shock phase of the disease. This hypothesis was supported by the production of lethal enterocolitis by administration of staphylococcic enterotoxin to chinchillas.[26] Pearce and Dineen[18] concluded that broad-spectrum antibiotics resulted in an overgrowth of staph in the gastrointestinal tract and that the staphylococcus caused pseudomembranous enterocolitis. It is very significant that their series included nonfatal cases of diarrhea with stool cultures of pure staph, therefore resting upon the dubious thesis that staphylococcic enteritis and pseudomembranous enterocolitis are the same disease. Eiseman[7] made this same assumption in reporting treatment by fecal enemata. All four of his cases had severe diarrhea: a feature not at all constant or even prominent in pseudomembranous enterocolitis. The predominant opinion obtained by review of the literature does not favor the theory that the staphylococcus (micrococcus pyogenes) causes pseudomembranous colitis. Many authors[4,8,11,14,25] have failed to find positive staphylococcic stool cultures in this disease.

Clinical Management

Treatment of pseudomembranous enterocolitis involves early recognition and rapid, forceful supportive therapy. Pearce and Dineen[18] state that the survivors receive supportive treatment and erythromycin an average of 5.7 hours after onset. Cortisone[10,11,16,18] or corticotropin[3,21,22,25] or norepinephrine has also been recommended in shock phase.[10,11] The recommendation for use of norepinephrine should be carefully reconsidered, since on the basis of the pathologic process it is probably contraindicated, for more spasm in the arterioles adjacent to the thrombotic mucosal capillaries might be expected to advance the necrotic process.

Surgery

More attention should be directed toward determination of the presence of peritonitis secondary to perforation or necrosis of the bowel wall having advanced to the stage of bacterial migration so that extirpative surgery can be employed as a lifesaving attempt.

Although pseudomembranous (necrotizing) enterocolitis has an extremely high mortality, and despite the frequent autopsy findings of perforation and peritonitis, the literature contains very few suggestions that direct surgical approach may have value in any phase or stage of the problem. In a discussion of the paper by van Prohaska,[21] W. C. Bartlett described operating on a case 24 hours after onset of shock. Gangrene and multiple perforations of the entire small bowel and right colon were treated by resection and anastomosis of the upper jejunum to transverse colon. His patient lived eight months.

Kay[11] advised operation to differentiate between high obstruction after gastrectomy and pseudomembranous enterocolitis; however, he did not suggest extirpative therapy of the enterocolitis. Killingback[12] advised wide resection of the diseased bowel. After initial attempts in earlier series had failed because of leakage at all anastomoses, he recommended a proximal and distal colostomy and later closure. Four survivors were reported from seven cases, all of whom were operated upon.

Differential Diagnosis

Staphylococcus

Staphylococcus (micrococcus pyogenes) will not grow well on routine eosin methylene blue-culture media, due to overgrowth of other bacteria. Therefore, stool cultures must be made on blood agar or phenylethyl alcohol media.[16] However, in later studies,[4,25] particular attention has been properly given to this point.

Pseudomembrane

The pseudomembrane may actually occur in a variety of unrelated conditions and probably represents a means of the bowel reacting to certain toxic stimuli.[2] Altmeiter[1] found that of 155 patients with staphylococcic enteritis, only nine had autopsy-proven pseudomembranous enterocolitis. The Mayo Clinic series of Dearing and Bagenstoss[4] failed to relate staphylococcic infection and pseudomembranous enterocolitis with any regularity. They also noted that staphylococcic enteritis usually responded to proper antibiotic therapy, whereas pseudomembranous enterocolitis has always been rare and did not respond to treatment whether staph was present or not. Fowler[9] found staphylococcic enteritis was not associated with a pseudomembrane and considers it important to differentiate between staphylococcic enterocolitis and pseudomembranous enterocolitis. Penner and Bernheim[19] believe that infection follows onset of pseudomembranous enterocolitis, since infection is not present in the earlier lesion.

Dr. Edward S. Judd, commenting on Markley's paper,[14] stated: "A rather sharp distinction can be made between modern enteritis due to staphylococcus aureus and the old well known pseudomembrane disease which the elder Finney described so beautifully before the turn of the century."

Cl Welchii

Cl welchii has been reported as a causative agent in necrotizing colitis,[12,17] a condition somewhat similar to pseudomembranous enterocolitis. One author named the condition enteritis necroticans and considers it the "Darmbrand" of North Germany and the same as "Struck" in sheep, a disease condition caused by Clostridium welchii and characterized by necrosis of bowel mucous membrane. Killingback[12] considers necrotizing colitis to be a separate entity from pseudomembranous enterocolitis.

Since pseudomembranous enterocolitis is a disease of unknown etiology, and staphylococcic enteritis is a specific disease entity, certain important differences may be enumerated which separate the two diseases.

Staph Enteritis

1. Usually follows broad-spectrum antibiotic therapy.
2. Profuse diarrhea.
3. Response to proper antibiotic (Erythromycin) and supportive therapy.
4. Generally recovers.
5. Pseudomembrane may or may not be present and is usually absent.
6. Diagnosis may be made by stool smears before culture identifies micrococcus pyogenes.

Pseudomembranous (Necrotizing) Enterocolitis

1. Commonly not related to antibiotic therapy — present as frequently before as after antibiotic era.
2. Minimal to no diarrhea.
3. Severe shock — sudden onset — collapse. Shock being a result and not cause of.
4. Failure to respond to therapy. Extremely high mortality.
5. Commonly follows surgery (usually gastric or colon).
6. May on occasion follow myocardial infarction.
7. Pseudomembrane may or may not contain staphylococcus (special cultures included).
8. Mucosal necrosis is an essential feature.
9. Cause unknown — no specific etiologic agent identified.

Additional Observations

If pseudomembranous enterocolitis is due to Staphylococcus (micrococcus pyogenes) in the absence of coliform bacteria, such as after antibiotic preparation, why should many cases involve the small bowel and even the stomach, where colon bacteria are not found, at least in any quantity?

The literature contains reports of enteritis of weeks' duration and of prolonged diarrhea. It seems evident that many varieties of enteritis have been classified as pseudomembranous enterocolitis without attention to the most specific criteria of pseudomembranous enterocolitis — the mucosal necrosis.

Postoperative Pseudomembranous Enterocolitis

The patient was a 68-year-old woman with peptic ulcer symptoms of one year's duration. Strict medical management produced no relief. Evening vomiting of increasing volume developed over a three-week period. A bleeding episode then appeared, requiring three transfusions. Re-x-ray revealed a 1 cm. diameter posterior duodenal bulb ulcer with some pyloric obstruction.

Past history involved only a cholecystectomy for stones 11 years before and a few years of mild diabetes, well controlled on two Orinase tablets daily.

Gastrectomy for Ulcer

On February 3, 1964, a two-thirds (197 grams) gastrectomy was performed on a moderately hypertrophic stomach. A Bilroth II reconstruction was done with the duodenal stump closed against the pancreas.

Postoperative Sequelae

The immediate operative period was entirely uneventful. However, at 12 hours post operative, flatus and a small amount (a few cc.) of liquid stool were passed. Whereas this was rather remarkable, it was unimpressive at the time and no culture or smear was taken. A similar very small liquid-stool passage occurred twice more in the ensuing 18 hours. Twenty-four hours after surgery the temperature rose to 102 and 103 degrees, with a slightly tender abdomen. The serum amylase was normal. Intravenous chloromycetin was started empirically at 1.5 grams per day. Generalized abdominal tenderness of a moderate degree developed. Forty-eight hours after operation blood pressure dropped to 80 systolic. Serum sodium was 120 and chloride 81, in spite of the patient's having received polyionic maintenance solution. Urine output ceased.

She was given 250 cc. of 3-per cent sodium chloride. Pressure rose to normal. Urine began to flow and she was given another 250 cc. of the same solution. Her condition stabilized, but with persistence of abdominal pain, some rigidity and rebound. Ten hours later shock again appeared with no electrolyte disturbance. Two units of plasma were rapidly given, also 500 mg. of hydrocortisone intravenously. The blood pressure returned to the normal 120 and remained stable. She was then given two more units of plasma, and additional diagnostic efforts were undertaken.

The abdomen was tapped with a 190-polyethylene tube threaded through a 15-gauge needle. Foul-smelling gas was obtained as soon as the stylet was removed from the needle. On the possibility of having entered the colon, the abdomen was tapped in another area with the same result of foul odor. A few cc. of brownish peritoneal fluid were obtained, and a gram stain revealed staphylococci with a few gram-negative rods.

Exploratory Laparotomy

On February 6, 1964, the third postoperative day, exploratory laparotomy was performed on the diagnosis of peritonitis, cause undetermined. The first view was a gangrenous transverse colon. Thereupon, the mid-colic vessels were carefully inspected and found to pulsate as far as the more terminal branches. Further exploration revealed patchy areas of gangrenous necrosis in the right and left colon. There was no involvement of the small bowel or stomach pouch and minimal if any involvement of the rectosigmoid a few inches above the peritoneal reflection. One or two hundred cc. of watery brownish fluid were in the peritoneal cavity. Foul odor was evident, and it was obvious that the colon was in an advanced stage of patchy necrosis with nearly total involvement of the transverse colon. No obvious areas of free perforation with fecal leakage were evident. The necrotic colon wall was, therefore, still sufficiently intact to retain the content of the lumen from free leakage. There was no appreciable distention of bowel. The clinical diagnosis of pseudomembranous enterocolitis was verified by the pathologist upon removal of the bowel.

The colon was removed from terminal ileum to rectosigmoid. A terminal ileostomy was made and a distal colostomy directly above the pubis achieved a mucous fistula of the distal segment. Vital signs remained surprisingly stable. The patient received three units of plasma on the operating table.

Pathologic Examination

The intestine was 90 cm. long with a total fluid content of 1500 cc. containing shreds of tissue compatible with mucosa. After cleaning the mucosal surface, one fourth of it appeared to be denuded. This included several wide areas in the cecum, transverse colon, and descending colon.

The microscopic examination showed dense inflammatory reaction with the muscle wall intact in most areas; section of the loose membrane revealed what appeared to be necrotic mucosa with many bacteria, the majority being of coccal form.

Diagnosis: "Pseudomembranous enterocolitis or staphylococcal colitis."

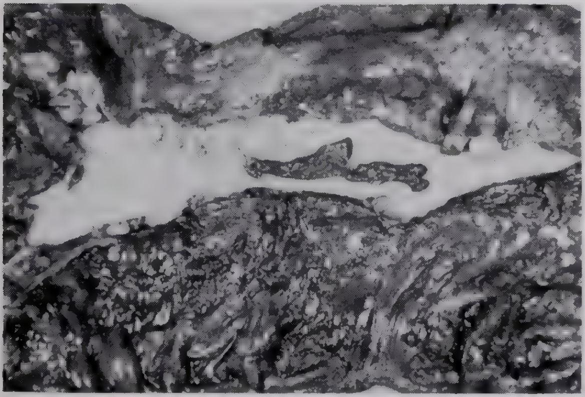

Fig. 1 — Photograph of gross specimen

Bacteriologic Examination: "Abdominal fluid from preoperative diagnostic paracentesis and from bowel wall reveal gram-positive cocci and a few gram-negative rods. Hemolytic coagulase positive staph aureus and pseudomonas aerugenosa on culture. The staph is sensitive to all tested antibiotics with the exception of penicillin, gantrisin, and polymyxin B."

Convalescence

Unipen was given parenterally, two grams per day, and also in divided doses into the mucous fistula of the distal sigmoid. By three weeks postoperative, pseudomonas was the only positive culture from both abdominal wound and rectal stump. Therefore the patient was put on Coly-Mycin. In about another week, the vaginal and perianal areas were obviously infected with a fungus. Culture revealed Candida albicans. This was treated locally with Fungisone lotion. The Coly-Mycin was discontinued at two weeks. The antifungal treatment continued for an additional two-week period, followed by complete clinical clearance. Finally, the bacterial flora of the mucous fistula of the distal colon returned to essentially normal distribution of bacteria except for a modest quantity of fungus. Suppositories of Mycostatin were inserted daily into the distal colon. The ileostomy output was of mushy stools with no abnormal quantity.

Smoldering Colitis

A smoldering colitis remained in the distal stump between the level of the peritoneal reflection and the mucous fistula, a distance of approximately six to eight inches. This was examined frequently by sigmoidoscope both through the mucous fistula and the anus. The rectal region remained entirely normal. The distal colon was treated four times daily with Medcort enemas, a solution of methyl cellulose and cortisone. Liver function survey failed to reveal any abnormality. Intravenous urography showed normal function and contour of the urinary collecting system. Urinalysis revealed only a few pus cells.

Pseudomonas

The patient was discharged on March 27, 1964,

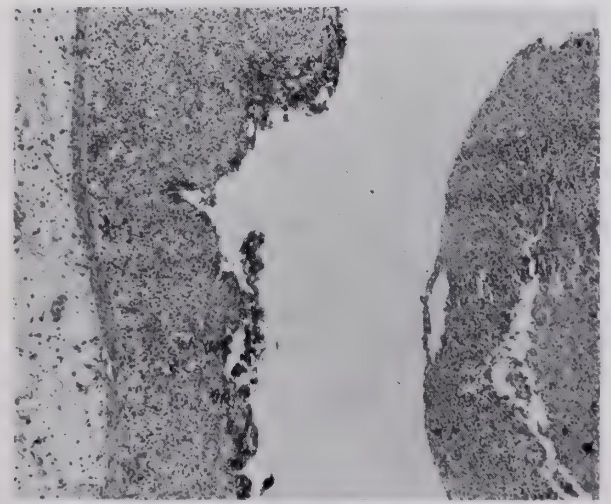

Fig. 2 — Representative microscopic sections

approximately eight weeks after her gastrectomy.

She was readmitted on April 4, 1964, because of return of low-grade fever, disorientation, and marked anorexia. On the thesis that she might have a residual intra-abdominal undiscovered abscess, she was treated with chloromycetin, 1.5 grams daily, and Unipen, 1.5 grams daily, for 10 days. Her temperature subsided within two days. As the mucous fistula revealed slight redness of the mucous membrane, cortisone enemas were reinstituted, and at the end of 10 days the bowel appeared entirely normal, with the usual dry sticky mucous. Urinalysis revealed no pus cells, but a culture showed 100,000 colonies of pseudomonas per cc. This was treated with streptomycin. Intravenous pyelogram showed no areas of statis, stones, or other abnormalities. She was discharged on Mandelamine, ½ gram q.i.d. to be continued indefinitely. Much improved the patient was again discharged on April 27, 1964.

Follow-up Observations

One month later proctoscopy was entirely negative from both directions, hemoglobin normal, white count 8250, and a weight gain of two pounds. On August 3, four months after the gastrectomy, six weeks after final discharge, the patient suddenly expired. At autopsy there were no abscesses within the abdomen or liver. The kidneys showed many irregular abscesses and papillary necrosis. Smears revealed pus cells and gram-negative rods. Both the small and the residual colon appeared normal. The lungs showed minimal pulmonary edema and congestion. The presumptive diagnosis was that of gram-negative septicemia with sudden shock. In retrospection it was found that in another location a urinalysis two weeks prior to death revealed a packed field of pus cells. This finding was never treated.

Clinical Conclusion

Early intensive and broad antibiotic coverage seemed essential but brought on a series of successive problems: the overgrowth of pseudomonas and the Candida-albicans problem. Whereas erythromycin is ordinarily considered the antibiotic of choice, there was obvious and massive peritoneal soilage by migration of bacteria through the gangrenous bowel wall; and upon the anticipation of abscess development in the face of infection that was not purely staphylococcal, the more broad coverage was elected.

Since small bowel and distal sigmoid appeared to be free of the disorder, and since nearly the entire colon needed sacrifice because of irreversible necrotic changes, an ileostomy and separate distal colon mucous fistula were performed in the anticipation of later re-establishment of bowel continuity by an ileosigmoidostomy. From the standpoint of bowel recovery that actually occurred, this could have been achieved.

The diagnostic abdominal tap removed any question of the urgency of reoperation three days after the gastrectomy by obtaining foul smelling gas from the free peritoneal cavity and a smear of fluid containing both cocci and gram-negative rods.

The employment of mucous fistula affords an excellent means of both treatment and inspection of the partially involved distal colon.

In view of the highly fatal outcome of this fulminating type of pseudomembranous enterocolitis, some future cases may be permanently salvaged by early resection of obviously necrotic bowel with a plan for restoration at a later date. If at laparotomy gangrenous areas are not present, treatment of choice should probably be continuation of medical management.

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The man who spends his life building walls rather than bridges has no right to complain if he is lonely. — Mills Warrior

The Amputation Site in the Lower Extremity

Regard for the Vascular Efficiency

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THE EFFICACY of the circulation is the important consideration in the selection of a site for amputation. After the amputation has been performed, the circulation in the stump is subject to the same problems as that of the other extremity.

When amputation is required for trauma, Marmor and Sollars[1] recommend that as much as possible of the extremity be saved in the initial surgery, and that any revision be left for a subsequent procedure.

The greatest number of amputations are performed for some type of peripheral vascular disease,[2] and approximately 70 per cent[3,4] are in elderly patients. In the present day of reconstructive vascular surgery every effort should be made to salvage the entire limb; however, if this is not possible, determination of the proper amputation site should be given consideration. In addition to providing an adequate stump for use of a prosthesis, the surgeon must be aware of the rehabilitative facilities which are available to his patient.[5]

Criteria for Determining the Amputation Site

In doing an amputation, it is hoped that the stump can have a maximal functional length with the best possible skin covering, and hence possess the best odds for fitting the prosthesis and successful rehabilitation.

Below the Knee Amputation

Adequate collateral circulation is most frequently associated with a slow onset of the disease process or a more distally lodged embolus if one is present.[6] The criteria for doing an amputation below the knee[7] are indicated in Table 1.

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TABLE 1

Criteria for Below the Knee Amputation[7]

Slow Onset of Disease Process
Palpable Femoral Pulse
Functional Knee
Unaffected Skin to Mid-Leg
Good Bleeding in Skin and Muscle at Amputation Site
Hope of Rehabilitation

Above the Knee Amputation

Sudden occlusion together with the lack of femoral pulsation usually indicates that the collateral circulation has not had time to develop, and it has been observed[6] that this condition exists frequently in patients with a cardiac lesion or low blood pressure insufficient to force its way through the collaterals. At the time of surgical operation, if the muscle is pinkish gray, bleeds poorly, and does not contract, surgery must be performed at a higher level.[4] Other criteria[7] are indicated in Table 2.

TABLE 2

Criteria for Above the Knee Amputation[7]

Sudden Onset of Arterial Occlusion With:
- Weak or Absent Femoral Pulse
- Low Skin Temperature
- High Venous Filling Time
- Evidence of Ischemia
- Poor Bleeding at Amputation Site

Embolic Occlusion and Gangrene

Prosthesis

If the patient can use an artificial limb without overexertion, a prosthesis is indicated. There have been some instances[8] in which the use of a prosthetic device has provided an improvement in circulation. If the proper criteria for doing an amputation are not observed, there may be a breakdown of the skin, edema, and a variety of undesirable complications.

Measuring the Efficiency of the Circulation

Each method of measuring the circulation gives a different evaluation; no one of the following methods is adequate for sole evaluation of the peripheral blood flow.

The Oscillometer

The oscillometer[9] measures the pulsatile change of volume in all the tissues under the cuff with each heart beat. It is easily used in a ward and does not require a basal condition.

Skin Thermometry

Skin thermometry using contact thermocouples taped to the skin is a simple method of assessing the ability of the sympathetic system to respond to vasodilating stimuli. The thermocouples are usually attached to the big and little toes and the sole and dorsum of the foot. Skin thermometry is not a convenient clinical tool, however, because it requires a constant-temperature room in order to provide an accurate reading.

Arteriography

The injection of contrast media into the femoral artery and the observation of the vascular outline are valuable in detecting evidence of collateral circulation.[10] This is the best method of graphically portraying the peripheral circulation.

*Plethysmography**

Venous occlusion plethysmography is performed by enclosing the extremity in an air or watertight box, occluding the venous return, and measuring the volume change in the box which corresponds to the arterial inflow of blood. An erroneous plethysmogram will be obtained if the venous return is not completely arrested. The patient must be in a basal condition and in a constant-temperature room. Plethysmography provides an excellent picture of the sympathetic response; it is the best method of assessing a total arterial inflow in any given segment.

Interpretation

Some of the composite circulatory indices that may be expected in the lower extremity with a room temperature of 26 ± .5 degrees C. during rest and indirect heat are indicated in Table 3.[9,11] The use of indirect heat serves to demonstrate the ability of the sympathetic system to respond to stimuli.

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*See Test Your Word Score Page 943.

Plethysmography Values

The plethysmographic values during the resting state are self-explanatory, and when values fall below these figures the arterial inflow is considered to be deficient. A minimal satisfactory sympathetic response of the circulation with indirect heating would be an approximate increase of two times the control value in the calf and three times the control value in the foot.

Oscillometric Indices

The oscillometric indices are based on the resting state only; change in the oscillometric index is not of stable diagnostic value following indirect heat. When the oscillometric index falls below "trace" at the instep, the circulation is considered to be inadequate for wound healing in the foot.[9]

Skin Temperature

Skin-temperature increases following indirect heat should go beyond 32 degrees C. in both the foot and the calf to indicate minimal sympathetic response of the circulation. Increase in temperature will generally exceed this figure by two to four degrees C. in both the foot and the calf.

In all instances indicated in Table 3 the smaller values are minimal, and it must be remembered that the values will vary in individuals and also as influenced by ambient temperature. These minimal values are at a level below which some form of surgery would probably be indicated if found in more than one of the methods which have been discussed.

Summary

Peripheral circulation is the primary consideration of amputation site. If amputation is performed, the circulation in the stump is subject to the same problems as that in the other extremities. The site of amputation may be selected in different ways depending

TABLE 3

Circulatory Indices in the Lower Extremity
During Rest and Indirect Heating.
Room Temperature 26° ± .5° C.

Normal Resting Indices	Minimal Indices Following Indirect Heating***
Plethysmography	
Foot	
1 to 3 cc./100 cc. tissue/minute	3 times control value
Calf	
1 to 2 cc./100 cc. tissue/minute	2 times control value
Oscillometry*	
Instep	
Trace to 1/2	
Above Ankle	
1/4 to 2-1/2	
Below Knee	
1/2 to 4	
Skin Thermometry	
Toes	
26° ± 2° C.	32° C.
Calf	
30° ± 2° C.	32° C.
Arteriography**	
Observable Channels	

*Oscillometric indices listed range from value required for slow ulcer healing to those necessary for normal walking.

**Room temperature designation not applicable.

***Indirect heating: Diathermy to abdomen or immersing hand in hot (43° to 45° C.) water.

on whether the amputation is traumatically caused or is a result of peripheral vascular disease.

Oscillometry, skin thermometry, arteriography and venous-occlusion plethysmography are all methods of assessing the efficacy of the peripheral circulation. Each tells a different part of the story. Of the four, oscillometry is the most easily used clinically. Arteriography is of particular value in assessing collateral circulation. Venous-occlusion plethysmography is the best method available for determining the total inflow of blood into a given area.

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4. Record, E. E.: Surgical Amputations in the Geriatric Patient. J Bone Joint Surg 45:1742, 1963.
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6-11 May be secured from the author or the reprints.

IT'S THE LAW

Hospital and Doctors not Liable in Patient's Death from Heart Disease

The administrator of the estate of a deceased patient was not entitled, in a suit against a hospital and two doctors, to recover damages for her death from heart disease, where there was no evidence that the negligence, if any, on the part of the hospital or the doctors was the cause of her death, the Court of Appeals of Kentucky ruled.

About a year before her death, the patient had been treated and hospitalized for pains in her arm, shoulder, and chest, and for shortness of breath. When her trouble recurred, she consulted a doctor who referred her to the hospital. That day she was seen by one of the two doctors and two days later by the second one. The patient died the morning after she had seen the second doctor.

An autopsy disclosed a hardening of the arteries of the heart, a necrosis of a heart muscle, and an apparently severe hardening of one of the arteries to the brain.

The evidence of negligence was unconvincing, the court said. The doctor who treated the patient for her heart trouble a year before her death testified that there was no one sign that could be associated with heart disease and nothing else. If it was assumed that the evidence established negligence, there was still no evidence that the negligence was the proximate cause of the patient's death.

Two doctors gave testimony critical of the treatment the patient received in the face of her symptoms and stated the opinion that she might have survived if she had received proper treatment for her condition. However, both witnesses admitted that there was no way they could conclude that she would have survived if she had had the treatment they recommended and neither would say that her failure to get that treatment caused her death.

Burke v. Miners Memorial Hospital Association, 381 S.W.2d 758 (Ky., May 29, 1964; rehearing denied, Oct. 2, 1964) — Citation.

The Vision Interference Indicator*

Device
for
Teaching
Tonometry

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Milwaukee, Wisconsin
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Washington, D. C.

UNTIL RECENTLY, the Schiotz tonometer, which measures the intraocular pressure, was primarily used by ophthalmologists. As the prevention of blindness from glaucoma is dependent upon early recognition and therapy many medical schools now include tonometry in the teaching curriculum for the undergraduate. The internist and general practitioner should screen for glaucoma.

In the case of open-angle glaucoma, by the time the patient is aware of symptoms, irreversible damage to the optic nerve may be found on the first visit. The majority of open-angle glaucoma patients have minimal or no complaints relating to their glaucoma and usually present themselves only for a change of glasses. Ophthalmologists routinely perform tonometry as a part of the eye examination. The table shows what the tonometry screening tests will yield as compared with other screening tests that are considered routine.

Development of the First Mannequin

Students have been trained in the technique of tonometry by using a test block and then by measuring the intraocular pressure in the eye of another student. To facilitate training and obviate apprehension, however, a mannequin was developed by the Neurological and Sensory Disease Service

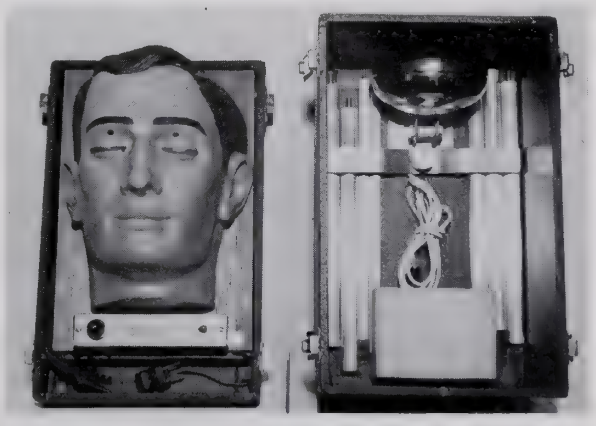

Fig. 1 — Take-apart assembly dismounted and housed in cover of carrying case. The portable case measures 14x9x9 inches and weighs approximately 17 pounds complete. Assembly is easily accomplished within a few minutes. The take-apart assembly may be eliminated in areas having a drop light, thus permitting a sealed-beam lamp with directing cone to serve as the source of light.

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*Exhibited at the Section of Ophthalmology, American Medical Association Meeting, June, 1964, San Francisco, California.

**Director, Glaucoma Referral Center, Marquette University School of Medicine and Assistant, Chief, Outpatient Service, Veterans Administration, Wood, Wisconsin.

†Public Health Advisor, Neurological and Sensory Disease Service Program, Public Health Service, U. S. Department of Health, Education and Welfare.

TABLE I

Disease and Population		Screening Test	Confirmed Diagnosis Per 1,000 Screened	%
Glaucoma:	General population over age 40	Tonometry	20 in 1,000	2.0
Diabetes:	General population	Blood tests	8 in 1,000	0.8
Cancer:	Females over age 25	Pap smear	4 in 1,000	0.4
Tuberculosis:	Adults	Chest X ray	1 in 1,000	0.1

The estimates noted in this table were compiled by the Neurological and Sensory Disease Service Program, Division of Chronic Diseases, Public Health Service, from several sources.

Program of the Public Health Service. This mannequin, which was tested at Marquette University Medical School, has realistic elastic lids with interchangeable eyes that have an elevated tension in one eye and normal tension in the other. This became a practical and popular training device and was subsequently offered to other medical schools.

Development of the Vision Interference Indicator

To ensure accurate readings the patient's eyes must remain still during the test; therefore he is asked to look at his thumb held overhead, thus maintaining the eyes in the straight-forward position as the tonometer is brought from the side and placed on the cornea of the eye being tested. Since the contralateral eye continues to regard the fixation area, no movement should be noted in the eye being tested.

The most common error in technique is related to inadvertent covering of the fixing eye of the patient by the hand or head of the person performing the test. This occurs as a result of improper placement of the hand holding the tonometer or the hand spreading the lids for exposure of the eye for the tonometer. To eliminate these common errors in technique during training we modified the apparatus to include photoelectric cells in the mannequin's lids with a beam of light that triggers a buzzer if blocked over both eyes at the same time (Figure 1). The second most common error noted is the improper separation of the eyelids which should be held open with the index finger and thumb against the orbital bone and not against the eyeball. This technique will eliminate a false positive test that would result if the finger of the examiner pressed on the globe.

"The Vision Interference Indicator" mannequin is an improved means of teaching tonometry to the physician or student and is available, along with the exhibit "Conserve Vision-Detect Glaucoma," for national, state, and regional medical meetings.

References

1. Information about the mannequin may be obtained from the Chief, Neurological and Sensory Disease Service Program, United States Public Health Service, Washington, D. C.

2. Funds and mannequin for the development of "The Vision Interference Indicator" were made Available by the Neurological and Sensory Disease Service Program, United States Public Health Service, Washington 25, D. C. Engineering and development of the apparatus was done by Eder Industries, Inc., Milwaukee, Wisconsin.

AGAMMAGLOBULINEMIA SYNDROME

This syndrome is characterized by constantly recurring infections of the respiratory system and almost complete absence of gamma globulin. The intra-muscular injection of human gamma globulins and the use of antibiotics provides benefit in these cases.

Durham, Robert H. — Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

Be discreet in all things, and so render it unnecessary to be mysterious about any.
— Wellington

Severe Anemia

as a Cause of

Heart Failure in Infancy*

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ROBERT C. SPECKHALS, M.D.**
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ALTHOUGH IRON deficiency anemia is reported to occur in up to 30% of infants,[1] it is unusual to observe hemoglobin concentrations below 5 grams per 100 milliliters of blood. This case report illustrates an unusually severe anemia which resulted in myocardial decompensation.

Case Report

A one-year-old white girl was admitted to Rice County District One Hospital because of listlessness and pallor. She had been irritable and fussy and had eaten poorly for several weeks. Since birth she had been fed only milk and mashed potatoes.

The patient, the fourth child of a 23-year-old woman, was delivered by cesarian section at 45 weeks normal gestation and weighed 4 kilograms at birth. At six weeks of age her weight was 5.5 kilograms and her hemoglobin 14.4 grams per 100 milliliters of blood. At 14 weeks of age she weighed 7.9 kilograms. The mother was not anemic, and there was no family history of hematological diseases. The child was not seen again by a physician until the date of admission, a lapse of over eight months.

Physical Findings

On admission physical examination revealed a well developed, extremely pale and listless child weighing 9.2 kilograms. The cardiac rate was 100 per minute, the respiration rate 36 per minute and the rectal temperature 100° F. There was no cervical venous distention. The pulmonary fields were clear. While cardiac rhythm was regular, a grade III/VI blowing holosystolic murmur was heard along the left sternal border, extending into the axilla. Palpation of the precordium revealed a hyperactive heart but no right or left ventricular heave. The liver and spleen were not palpable. Good pulsations were present over both femoral arteries. No peripheral edema was present. Neurological examination revealed marked generalized muscular weakness.

Laboratory Findings

The hemoglobin concentration was estimated to be 1.6 grams per 100 milliliters of blood; the hematocrit was 7.0% and the RBC 1.5 million. The peripheral blood smear showed hypochromasia and microcytosis (Figure 1). The mean corpuscular volume was 46.6 cubic microns; the mean corpuscular hemoglobin was 10.6 micro micrograms, and the mean corpuscular hemoglobin concentration was 23%. An electrocardiogram was normal. A routine urinalysis was negative for albumin, glucose and formed elements. Stools for occult blood and a direct Coombs test were negative. The total blood leukocytes and differential counts were normal.

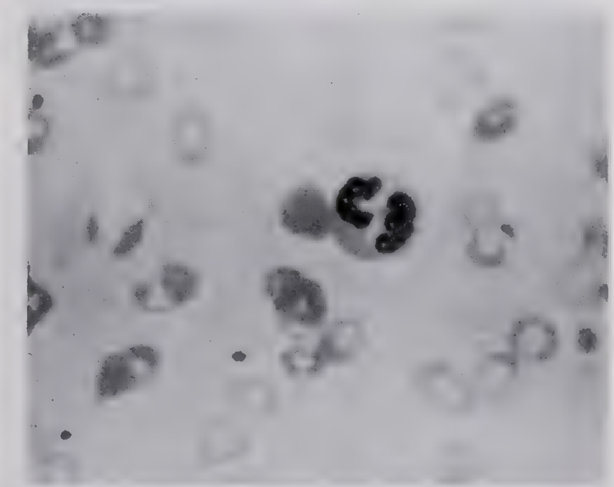

Fig. 1 — Initial peripheral blood smear. Hemoglobin concentration was 1.6 gm./100 ml. of blood and the hematocrit was 7.0%. There is marked microcytosis and hypochromasia. (Wright's stain x 1,000).

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*Read before the annual meeting of the Southern Minnesota Medical Association, September 10, 1965, Sheraton-Ritz Hotel, Minneapolis, Minnesota.

**Faribault Clinic.

Therapy

Oral iron therapy was begun with ferrous sulfate (60 mg. elemental iron daily). The following day, twenty-eight hours after admission, the patient suddenly developed myocardial decompensation manifested by a cardiac rate of 160 per minute, respirations of 72 per minute, and liver edge palpable 8 cm. below the right costal margin. A thoracic roentgenogram (Figure 2-a) revealed cardiac enlargement and pulmonary vascular congestion. The child was placed in an oxygen tent, digitalized and given a mercurial diuretic. A transfusion of 90 milliliters of packed red cells was administered 18 hours later. At the end of 24 hours all signs of cardiac decompensation had disappeared and no further blood transfusions were given. A thoracic roentgenogram five days later showed clearing of the pulmonary vascular congestion (Figure 2-b).

The response to therapy is summarized in Figure 3. The reticulocyte count increased rapidly following administration of oral iron and was accompanied by a progressive rise in hemoglobin concentration. A temporary depression of the reticulocyte count occurred following the transfusion of packed red cells.

The child continued to show improvement on adequate diet and oral iron therapy. On the seventh hospital day when the hemoglobin concentration was 8.3 grams per 100 milliliters of blood, and the hematocrit was 26.5%, the patient was discharged. Digitalis was discontinued on the 23rd day. The cardiac murmur disappeared by the 42nd day of therapy. At eighteen months of age the child had a normal hemoglobin concentration, no cardiac murmur, and a normal thoracic roentgenogram. At this time iron therapy was discontinued.

Discussion

Although serum iron determinations were not obtained, the striking response to oral iron therapy indicated by the reticulocytosis and by the increase in blood hemoglobin concentration is confirmatory evidence of iron deficiency anemia.

The effects of anemia upon the cardiovascular system and the occurrence of congestive cardiac failure have been well documented.[2,3] Cardiac manifestations seldom occur with hemoglobin concentrations above 7.0 grams per 100 milliliters of blood. Organic cardiac disease must always be considered in anemic patients who develop congestive myocardial failure, even when the hemoglobin concentration is below this level. In the case reported, treatment of the anemia resulted in a return to normal of the cardiac status.

Causes of Iron Deficiency

The four important causes of iron deficiency in infancy[1] are: (1) deficient iron stores at birth; (2) rapid growth rate especially of small or premature infants; (3) inadequate intake of iron; and (4) blood loss. Maternal iron deficiency is important only when the mother has a severe hypochromic anemia (hemoglobin concentration less than 7 grams per 100 milliliters of blood).[4] As small (less than 3000-gram) infants have less total iron at birth than large infants, their rapid growth rate predisposes them to hypochromic anemia. The influence of diet has been recognized for many years.

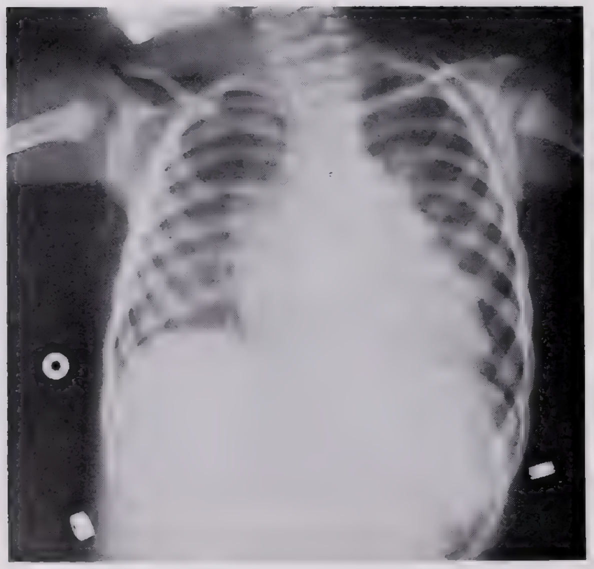

Fig. 2-a — Initial chest x-ray showing generalized cardiomegaly and pulmonary vascular congestion.

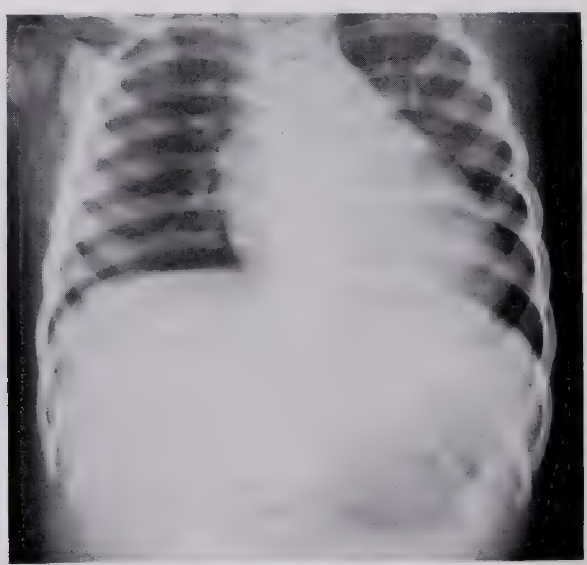

Fig. 2-b — Chest x-ray five days later showing clearing of the pulmonary congestion and a decrease in the cardiomegaly.

The most common diets include only milk, mashed potatoes and cereals, as in the case reported, and exclude meat and other iron-containing foods. Occult blood loss from the gastrointestinal tract was investigated by Hoag et al.,[5] utilizing radioiron studies. In thirteen infants with iron deficiency anemia they found that loss of whole blood in the stool varied from 7 to 107 milliliters over a three to four-week period. They did not elaborate on the cause of this blood loss.

Diagnosis of Iron Deficiency

The diagnosis of iron deficiency anemia is based upon an awareness of its possible occurrence, knowledge of susceptible infants, and appropriate laboratory studies. Hematologic studies show microcytosis and hypochromasia indicated by low red-cell indices. Stained smears of the peripheral blood confirm these findings and are more reliable when the anemia is severe, since the accuracy of hemoglobin determinations and erythrocyte counts is poor at low values. Thalassemia* and iron-loading anemias may have similar findings but can be differentiated by serum iron determinations. In iron deficiency the serum iron is low (less than 20 micrograms) and the total iron-binding capacity is increased.

Therapy for Iron Deficiency

The choice of iron-containing medication from the wide variety of medications now available for pediatric use can be easy if certain basic facts of iron therapy are kept in mind: (1) ferrous iron is better absorbed than ferric; (2) ferrous sulfate is the cheapest form of iron available; and (3) the response to ferrous sulfate is prompt and reliable. The therapeutic dose is 1.5 to 2.0 milligrams of elemental iron per kilogram of body weight, given three times a day. If preparations containing ferric iron are used, amounts greater than 2.0 milligrams per kilogram must be given. Response to adequate replacement therapy is prompt. Reticulocytosis occurs within five to ten days of treatment, followed by a rise in hemoglobin concentration. The latter is usually at normal level by two months. Therapy is continued for a month after normal hemoglobin concentrations are achieved, in order to improve body stores of iron. If no improvement occurs after one month of adequate therapy, iron administration should be stopped and the diagnosis re-evaluated, as the continuation of iron therapy over long periods may lead to hemosiderosis in patients with hemolytic or hypoplastic anemias. More important, other serious disorders may go unrecognized.

Transfusions are generally not indicated and may be dangerous in the presence of borderline cardiac compensation. If the hemoglobin concentration is below 4 to 5 grams per 100 milliliters of blood, it is usually safer to employ transfusions — preferably packed red cells. The amount of blood given should not exceed 10 milliliters per kilogram of body weight, as it is not necessary to raise hemoglobin concentrations above 7 to 8 grams per 100 milliliters of blood by transfusion. In the case reported, myocardial decompensation was first brought under control with appropriate medical therapy followed by immediate transfusion. Transfusion alone would probably have aggravated the cardiac failure and perhaps caused the death of the infant.

Summary

The case of a one-year-old infant with congestive myocardial failure on the basis of severe iron deficiency anemia is reported. The cardiac status returned to normal following appropriate therapy, and at 18 months

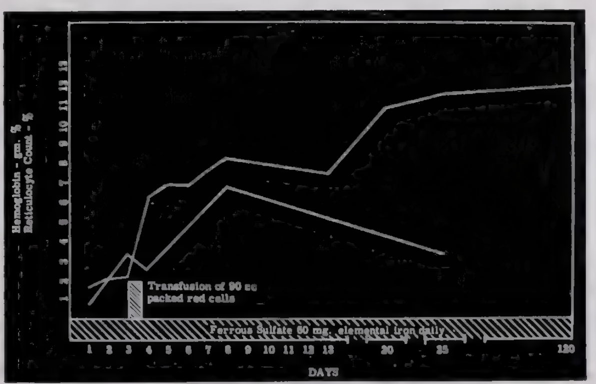

Fig. 3 — Response of hemoglobin and reticulocyte count to oral iron therapy. (Elemental iron 60 mg./day).

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*See Test Your Word Score Page 943.

of age the hemoglobin concentration was normal, and there were no cardiac abnormalities.

Iron-deficiency anemia in infancy may occur by any one or more of four mechanisms. These are: (1) deficient iron stores at birth, (2) rapid growth rates of small and premature infants, (3) iron-deficient diets and (4) blood loss. Hematologic studies reveal a hypochromic, microcytic anemia, a low-mean corpuscular hemoglobin concentration, low serum iron levels and an increase in total iron-binding capacity.

Ferrous sulfate is the drug of choice in iron-deficiency anemia. The indications for transfusion are presented, and the use of packed red cells rather than whole blood is recommended.

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Early Angela-Saxon Pharmacopeia

Brownwort: For disease of spleen, take roots of this same wort; pound it to small dust; give it to drink in light wine, therewith thou wilt observe a remarkable thing (i.e. a wonderful cure).

Mandragora: For headache, and in case that a man may not sleep, take the juice, smear the forehead; and the wort also in the same manner relieveth the headache; and also thou wonderest how quickly the sleep cometh. . . . For podagra, though it be very severe, take of the right hand of this wort and also of the left, of either hand by three pennies weight; reduce to dust; give to drink in wine for seven days; (the patient) will be healed, not only so that the swelling is allayed, but it also healeth the tugging of the sinews and wonderfully healeth both the evils."**

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*See Minnesota Med 48:1576, 1965.

**Payne, Joseph Frank, M.D. Oxon.: English Medicine in the Anglo-Saxon Times, Oxford at the Clarendon Press, 1904, p. 69-74.

The Tobacco Tyrant

Some things are much better eschewed than chewed; tobacco is one of them. — George Prentice

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The world does not require so much to be informed as reminded. — Hannah More

Communication Barriers Between Medical Students and Their Psychiatric Patients[*]

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SHEROD L. MILLER, M.S.W.[†]
FLOYD K. GARETZ, M.D.[‡]
Minneapolis, Minnesota

THE RESEARCH for this paper grew out of an interest of members of the staff of the Psychiatry Outpatient Clinic of the University of Minnesota Hospitals in the incidence of patients with psychiatric problems in a general medical clinic and in the evaluation of such patients. Our goal was to learn something of the percentage of patients in a general medical setting who indicate that they have psychiatric problems and to learn also something of the way in which such patients are evaluated.

In order that the reader will better understand the nature of this research, the authors believe that it will be helpful to describe the setting in which the research occurred. The Comprehensive Clinic Program is an attempt to provide the medical student with the experience of having overall responsibility for patient care. The student starts with the patient in New Medicine Clinic and participates in the evaluation and treatment of all his patients in the various specialty clinics. He comes with his patient to Psychiatry Clinic one-half day per week for the entire six months. Here through the mechanism of small group supervision and direct contact with staff social workers, psychologists and psychiatrists, he evaluates and in some instances provides psychotherapy for his patients.

Data

The data of this research were derived from two main sources. First, all patients in the study were asked to complete a simple, short questionnaire. The questionnaire was completed during the patient's first visit to New Medicine Clinic. After the questionnaire was completed, it was sealed in an envelope and was not available to examiners conducting the regular clinical evaluation of the patient.

The manner in which the patients answered the questionnaire led to classification of patients into several groups. A patient was considered to have indicated that he had psychiatric problems if he answered affirmatively any two of the questions which specifically referred to mental, emotional or psychological concerns. A patient was considered to have asked for psychiatric help if he answered affirmatively the question regarding his wish to see a social worker, psychiatrist or psychologist for help with his problem.

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[*] The authors wish to thank the many patients and hospital personnel who helped in this study.

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[†] Senior Psychiatric Social Worker, Outpatient Psychiatry Clinic, University Hospitals, Minneapolis, Minnesota.

[‡] Assistant Professor, Department of Psychiatry and Neurology, University of Minnesota Medical School, Minneapolis, Minnesota.

One sample of patients was accumulated in June and July, 1964. This sample consisted of 147 patients and was characterized by the fact that the medical students seeing these patients were just beginning their experience in the Comprehensive Clinic Program. A second sample of 71 patients was accumulated in September and October, 1964, after the students had passed the half-way mark in their experience in the Comprehensive Clinic Program.

The second kind of data collected for this research came from clinical records of the patients. The records of each patient in the study were reviewed carefully by one of the authors. Special attention was paid to (1) whether or not there was any mention in the current record of mental, emotional, family or psychological problems; and (2) whether or not there was a psychiatric referral or consultation and/or treatment in the psychiatric clinic. Review of the charts was begun approximately four weeks after the patient's initial visit in New Medicine Clinic.

From the information gathered from the clinical records, a classification of patient groups was made. If anywhere in the current New Medicine work-up there was mention of a psychiatric problem, it was considered that the examiner in that case had recognized the presence of a psychiatric problem in the patient. If referral or consultation occurred, either through the facilities in our own hospital or facilities elsewhere in the community, it was considered that the patient had been referred for psychiatric evaluation.

Results

Table 1 is a summary of results regarding the incidence of psychiatric problems in 218 patients in a general medical setting. The data of Table 1 suggest that there is a significant difference between the percentage of patients who report psychiatric problems on a questionnaire as compared to the percentage of patients in the same sample perceived by medical student examiners to have psychiatric problems. There is also a significant

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Name:
Address:
Date:

Dear Patient:

We ask your cooperation in answering the following questions just as you feel today. We hope that by so doing we can get a better understanding of your problems.

Answer Yes or No.	Yes	No
1. Have you been ill for a long time?	______	______
2. Did you have treatment for your illness before coming here?	______	______
3. Do you tend to worry a lot about your health or other matters?	______	______
4. Do you have trouble eating or sleeping?	______	______
5. Do you feel you have psychological problems?	______	______
6. Do you tend to cry a great deal?	______	______
7. Are you satisfied with your life?	______	______
8. Do you quarrel with others easily?	______	______
9. Have you been in trouble during the past year?	______	______
10. Are you very unhappy about anything which concerns your family, your job or relationships with people?	______	______
11. Do you want to discuss these problems with someone in the University Hospitals, namely:		
A. Social worker	______	______
B. Psychiatrist	______	______
C. Psychologist	______	______

Please enclose this in envelope, seal and give to nurse.

Figure — A Copy of the Questionnaire Used in the Study difference between the percentage of patients who asked for help as compared to the percentage of patients in the same sample who were referred for psychiatric consultation.

Table 2 is a summary of data with further breakdown of the sample in terms of age, sex and marital status.

Table 2 is a complex compilation of data and needs further explanation. The total sample of 218 patients was analyzed in terms of three variables: age, sex and marital status. Patients were divided into under age 49 and over age 49; male and female; married and unmarried. Then the data was examined in terms of the sub-groups of age, sex and marital status to determine the influence of these three variables on (1) the percentage of patients who indicated they had psychiatric problems, (2) the percentage of patients in whom psychiatric problems were recognized by the examiner, (3) the percentage of patients who asked for psychiatric help, and (4) the percentage of patients who were referred for psychiatric evaluation. There were more of the younger group, more females, and more unmarried patients in every category.

Percentage differences were calculated. For example (column one, line one of the table) 14 per cent more patients under age 49 indicated they had psychiatric problems than patients over 49. This difference was significant at the five per cent level. As another example, the difference in percentage between male and female patients who asked for psychiatric help was only three per cent. This was not a statistically significant difference.

Table 2 also has some other interesting aspects. If we consider two percentage differences, for example, we find that there is a three per cent difference between males and females who asked for help and a six per cent difference between male and female patients who were referred for psychiatric evaluation. The difference between six per cent and three per cent was not found to be statistically significant. However, considering the difference between males and females who indicated they had problems (12 per cent) and the difference between males and females who were recognized by an examiner as having psychiatric problems (31 per cent), this difference of 19 per cent is statistically significant.

Table 3 is a summary of data comparing

TABLE I

A Summary of Data Regarding the Incidence of Psychiatric Problems in 218 Patients in a General Medical Clinic

Patients indicated they had problems on a questionnaire	54%	p .01
Examiner recognized the presence of a psychiatric problem	32%	
Patients indicated they had problems and asked for help	26%	p .05
Examiners referred patient to psychiatry	17%	

TABLE 2

This is a summary of data regarding percentage differences when the sample of 218 patients was analyzed as to age, sex and marital status. The percentages shown in each of the columns designated age, sex and marital status refer respectively to the following: differences between patients under age 49 as compared to patients over 49; differences between male and female; differences between married patients and unmarried patients. The left hand column refers to the particular aspect of the data for which the percentage differences occurred. "Indicate" means patients indicated they had psychiatric problems. "Recognize" means examiner recognized the presence of psychiatric problems. "Help" means the patient asked for psychiatric help. "Referred" means the patient was referred for psychiatric evaluation.

	Age	Sex	Marital Status
Indicate	14% $p < .05$	12% $p < .1$	14% $p < .05$
Recognize	13% $p < .05$	31% $p < .01$	11% $p < .1$
Help	18% $p < .01$	3% $p < .5$	16% $p < .02$
Referred	21% $p < .01$	6% $p < .5$	13% $p < .05$

how patients answered the questionnaire and the course of the patient's evaluations. The data of Table 3 suggest that training and experience increase the student's ability to recognize psychiatric problems in their patients and also to better deal with these problems when recognized. Although none of the percentage difference in Table 3 reached statistical significance at the five per cent level, the consistency of difference of direction suggests that the difference might reach statistical significance, were the sample larger.

Conclusion

The following conclusions appear warranted from the data of this research: (1) previously reported clinical observations are confirmed in that a significant percentage of patients in a general medical clinic report or are perceived as having psychiatric problems. (2) There is a difference in the percentage of patients who report psychiatric problems on a questionnaire as compared to the percentage of patients in the same sample perceived by the medical student examiner to have psychiatric problems. This is thought by the authors to reflect difficulties of communication between students and their patients about psychiatric problems. Not all patients who asked for help with psychiatric problems were referred for psychiatric evaluation. The two major reasons for this are thought to be that students do not always recognize psychiatric problems and are not always aware of appropriate ways of dealing with such problems, even if they are recognized. (3) It appears that experience and training increase the medical student's ability to communicate with his patients regarding psychiatric problems and also to cope better with such problems when they are recognized. Both the percentages of recognition and referral increase with experience. (4) The problems of students in communicating with patients regarding psychiatric problems do not appear to result from stereotypes or preconceptions students might have about patients regarding age or marital status. It does appear, however, that medical students do perceive female patients as having more problems than male patients. (5) The review of clinical records by the authors revealed a total of 20 patients in groups I and II who had problems generally described as psychosomatic or psychological, such as ulcers, asthma, headaches, low back pain, etc. Since none of these patients were referred for psychiatric treatment by the student examiner, one may assume that the student examiners viewed these problems as organic rather than as having psychological implications. (6) The data of this investigation indicate the need for further explorations of methods and content of communication between student physicians and their patients. We particularly need to help students understand their patients in terms of personal, emotional, mental and family concerns.

Summary

This research is a study of 218 outpatients seen for initial medical evaluation in a general medical setting. The patients were seen by senior medical students under staff supervision. On a questionnaire 54 per cent of the patients indicated that they had psychiatric

TABLE 3

This is a summary of data comparing how patients answered the questionnaire and the clinical course of each patient's evaluation. "Inexperienced" refers to patients seen by "inexperienced" medical students (those in the first two months of experience in Comprehensive Clinic Program.) "Experienced" refers to patients seen by "experienced" medical students (those past the half way mark in their experience in the Comprehensive Clinic Program.)

Patients Indicated They Had Psychiatric Problems	Recognized by Examiner	Referred to Psychiatry
Inexperienced	49%	25%
Experienced	60%	37%
Patients Who Asked for Help		
Inexperienced	63%	39%
Experienced	76%	52%

problems, confirming other observations that psychiatric problems are extremely common in a general medical setting.

This research investigates communication barriers between medical students and their patients and finds that students frequently cannot communicate with their patients about psychiatric problems. However, as students become more experienced under supervision, their ability to communicate with patients improves.

Frequent areas of difficulty for students appear to be with patients who have psychophysiologic disorders. Also, students tend to over-react to problems in female patients.

Papyrus Ebers[*]

To Eliminate Tapeworms in Ancient Egypt

Wormcakes were recommended first. One cake was composed of Herbs-of-the-Field and Natron, baked into a cake with Cow's Bile. Another was compounded of Herbs-of-the-Field and Heart-of-the-mesa-Bird, along with Honey, Wine, and Sweet Beer. Or a draught could be used.

Red-lead	1
gentet-plant, nesxi-corn, ta-bread	1
Petroleum	1
Sweet Beer	1

Stir, powder, strain, and take for one day.

And desperate cases could resort to a poultice:

Resin-of-Acanthus	1
Blossoms-of-the-Peppermint	1
Wild Lettuce	1
t'as-plant	1

Stir, mix into one, and apply as a poultice to the Body of the Man or Woman.

That some of the patients after a course of treatment on the lines indicated should complain of anal discomfort is not a thing for wonder. Consequently it occasions no surprise to find a large section devoted to relieving this sequela. As usual the thing was done thoroughly. Internal remedies were first prescribed:

Remedy to Cool the Anus

Onion-meal	1/32
Tail-of-a-Mouse	1/32
Honey	1/4
Water	1/3

Strain and take for four days.

A suppository was next recommended:

Fat-of-the-Antilope	1
Caraway	1

Roll into a Pill and put in the Anus

Another Remedy Against Sores in the Anus

Egg-of-the-Goose	1
Guts-of-the-Goose	1

Clap on the anus.

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[*] Byran, Cyril: The Papyrus Ebers. D. Appleton and Company, New York, 1931, p. 56-58. See Minnesota Med 49:859, 1966.

Anti-Nuclear Antibodies

THE PURPOSE of this study is to report the incidence of circulating anti-nuclear antibodies in a variety of clinical conditions. The demonstration of such antibodies may aid in the diagnosis of certain diseases and possibly indicate an auto-immune mechanism operative in some of them. The need in diagnostic laboratories for a new immunochemical method to detect the anti-nuclear antibodies may be summarized as follows:

The conventional lupus erythematosus clot test has been negative in a considerable number of histologically proven systemic lupus erythematosus cases. Dubois[1] stated that such clot tests had been positive in 50% of systemic lupus erythematosus patients. Lupus erythematosus cell formation is a complex immunobiological event which can be interfered with by a number of factors, such as anti-complementary effect and the

TABLE 1
Collagen Disease Group: Results with Fluorescent Anti-nuclear Antibody Test Technique

Diagnosis	No. of Cases	No. of Positive	% Positivity
Systemic Lupus Erythematosus	44	40	90
Discoid Lupus Erythematosus	54	32	59
Rheumatoid Arthritis	74	26	35
Rheumatic Fever	28	14	50
Polyarteritis Nodosa	8	6	75
Scleroderma	5	1	20
Dermatomyositis	4	1	25
Idiopathic Vasculitis	2	1	
Sjögren's Syndrome	2	1	

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*Presented at the A.M.A. Annual Meeting in San Francisco on June 23, 1964.

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in Various Diseases*

MUHARREM GÖKCEN, M.D., Ph.D.**
WILLARD C. PETERSON, JR., M.D.†
CAROL EHRNST, B.S.‡
Minneapolis, Minnesota

inhibitors of the patient's blood. The factor which is responsible for the lupus erythematosus cell formation is an auto-antibody directed against the DNA-protein complex of the nucleus. Other auto-antibodies such as anti-histone, anti-DNA, and anti-soluble nucleoproteins may be present in the absence or presence of the lupus erythematosus factor; but these do not seem to participate in lupus erythematosus cell formation. The present technique, fluorescent anti-nuclear antibody, appears to overcome these difficulties in that it is not affected by the interferences in the patient's blood or otherwise, and it can detect all the auto-antibodies directed against the nuclear constituents. Furthermore, in the auto-immune-group diseases, anti-nuclear antibodies have been more commonly encountered, so that such a method might constitute a broad-spectrum, auto-immune screening test.

Materials and Methods

The sera of 612 patients were sent to our laboratories by various services of the University of Minnesota Hospitals, Glenwood Hills, Fairview, and St. Mary's Hospitals of Minneapolis. The fluorescent anti-nuclear antibody test was run once in the majority of cases, with the sera of 132 blood bank donors serving as controls. In almost all cases, the clinical diagnosis was not known at the time that the test was performed; the diagnosis listed in the present study was obtained by chart reviewing at a later date. The fact should be stressed that a few of these patients were diagnostic problems and the diagnosis taken from the chart might not be the accurate final diagnosis.

The method of the fluorescent anti-nuclear antibody (FANA) test has been published in detail by one of us.[2] Briefly, the technique may be summarized as follows: Blood smears of normal individuals were used for the source of leukocyte nuclei. The smears were incubated with patients' sera to let the antigen-antibody reaction take place; then they were washed in a suitable buffer solution to eliminate unbound non-antibody proteins. Finally, the smears were treated with fluorescent-labeled anti-human gamma globulin which would detect the gamma globulin antibodies bound to the nuclei of leukocytes.

TABLE 2
Anti-nuclear Antibodies in Liver Disease

Diagnosis	Positive	Total
Laënnec's Cirrhosis	7	13
Postnecrotic Cirrhosis	6	8
Plasma Cell Hepatitis	4	5
Infectious Hepatitis	2	5

TABLE 3
Anti-nuclear Antibodies in Hematological Disorders

Diagnosis	Positive	Total
Auto-immune Hemolytic Anemia	2	5
Secondary Hemolytic Anemia	0	10
Idiopathic Thrombocytopenic Purpura	3	7
Anaphylactoid Purpura	0	3
Idiopathic Neutropenia	1	1
Splenic Neutropenia	1	1
Cyclic Neutropenia	1	2
Infectious Mononucleosis	0	2
Chronic Lymphatic Leukemia	0	4
Multiple Myeloma	0	1
Lymphoma	0	6

TABLE 4
Anti-nuclear Antibodies in Skin Conditions

Diagnosis	Positive	Total
Sunlight Sensitivity	0	18
Erythema Nodosum	0	2
Erythema Nodosum with Carcinomatosis	1	1
Raynaud's Phenomenon	1	3
Serum Sickness	0	2
Drug Reaction	0	2

TABLE 5
Anti-nuclear Antibodies
in Neuropsychiatric Cases

Diagnosis	Positive	Total
Multiple Sclerosis	5	14
Polyneuritis	2	12
Radiculitis	2	4
Epileptic Conditions	0	2
Arachnoiditis	0	4
Chronic Brain Syndrome	0	3
Myasthenia Gravis	0	1
Hernia of Lumbar Disc	0	1
Muscular Dystrophy	1	1
Depression	0	4
Schizophrenia	1	3
Psychoneurosis	2	11
Senile Dementia	0	1
Alcoholic Encephalitis	1	1

Results

The results are summarized in Tables 1-8. Five per cent of the 132 blood-bank donors showed a positive reaction. Table 1 includes the collagen disease group which exhibits a very high incidence of positive anti-nuclear antibody test:

Systemic Lupus Erythematosus

Ninety per cent of 44 cases were positive. Four negative cases were in complete remission. Although the lupus erythematosus clot test was not run concurrently with the fluorescent anti-nuclear antibody test, almost all of these 44 cases were a diagnostic problem with repeatedly negative lupus erythematosus clot tests. The fluorescent anti-nuclear antibody test can become negative during the course of immunosuppressive therapy if an adequate remission takes place.

Discoid Lupus Erythematosus

Fifty-nine per cent of 54 cases were fluorescent anti-nuclear antibody test positive. All of these cases had a negative lupus erythematosus clot test. Positive cases were predominantly women. Detailed study in many of these patients had been published.[3]

Rheumatic Fever

There was fifty per cent positivity in 28 patients who were mostly at the recurrent active stage of the disease.

Rheumatoid Arthritis

Thirty-five per cent of the 74 cases were positive, and positive cases were again predominantly females who showed a high titer rheumatoid factor in the sera. Positive cases also tend to have more systemic manifestation of the disease, i.e., fever, muscular pain, pleuritis, etc. Two of the positive patients' courses were complicated with diffuse vasculitis while they were on corticosteroid therapy. Another two positive patients complained of dryness in the mouth and in the eyes with mild swelling of the parotid glands. These two cases might be classified as Sjögren's syndrome.*

Other Collagens

Polyarteritis nodosa cases showed a 75% incidence of positivity. Negative scleroderma cases had the disease localized in the skin.

Liver Diseases

Table 2 summarizes the results: postnecrotic cirrhosis and plasma cell hepatitis cases combined exhibited very high percent positivity — 80%. Laënnec's cirrhosis showed 50% positives.

Blood Diseases

Results are summarized in Table 3. Although a small number of cases were included in this group, a significant number of positivities were observed in idiopathic thrombocytopenic purpura and auto-immune hemolytic anemia.

Skin Diseases

Conditions listed in Table 4 were negative, except one case with Raynaud's phenomenon and one of erythema nodosum. The latter case was a woman who received deep X-ray therapy for a carcinoma of the uterus and developed fever and erythema nodosum one day later. Her lupus erythematosus clot test was also positive.

Neuropsychiatric Disorders

A significant number of patients with multiple sclerosis (Table 5) were positive, as reported earlier in other groups of patients.[4] Occasional positivities were recorded in cases of acute polyneuritis (Guillain Barré syndrome) and radiculitis.

Metabolic Conditions

As seen in Table 6, the cases of nontoxic goiter were positive.

TABLE 6
Anti-nuclear Antibodies
in Metabolic Conditions

Diagnosis	Positive	Total
Nontoxic Goiter	3	4
Hypothyroidism	1	5
Thyroiditis	1	6
Hyperthyroidism	0	3
Diabetes Mellitus	1	8
Arteriosclerosis	2	13

Various Other Diseases

Table 7 shows a group of various diseases which exhibited a definitely higher percentage of positivity than a normal control group. Among those, the following conditions deserve to be mentioned: All three positive patients with bronchial asthma were nonallergic after the age of forty and had high blood eosinophils and negative lupus erythematosus clot tests. Three of the fifteen cases with glomerulonephritis were interesting: One had a positive lupus erythematosus clot test but showed no other systemic involvement of his disease. The second was a young woman with chronic nephritis and a negative lupus erythematosus clot test. The third patient was also a young female with a negative lupus erythematosus clot test, who probably had lupus erythematosus. All four positive fluorescent anti-nuclear antibody test cases of diffuse carcinomatosis were in women, being primarily either of the breast and/or of other female organs. Almost all had pleural effusion without tumoral involvement, hemolytic anemia, fever and joint manifestations. It is also interesting to note the presence of positive cases with pyelonephritis and regional enteritis. One of two positive pericarditis patients developed nephritis a few months later, and the diagnosis was changed to systemic lupus erythematosus. Her lupus erythematosus clot tests were negative.

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*See Test Your Word Score Page 943.

Cases with negative fluorescent anti-nuclear antibody test, who were not included in any of the tables, were diagnosed as having acute bronchitis, pneumonia, cholecystitis, upper respiratory infections, hypertension, etc.

Comment

The high incidence of positive anti-nuclear antibodies in the collagen disease group is expected in view of the auto-immune process demonstrated in such a disease as systemic lupus erythematosus. It is, however, interesting as well as surprising to find 50% positivity in rheumatic fever or in rheumatic heart disease cases. The relationship between rheumatic fever and beta streptococcic infections has been well documented. Kaplan[5] recently reported that human heart muscle and the wall of streptococci possessed common antigens.

TABLE 7
Anti-nuclear Antibodies
in Various Conditions

Diagnosis	Positive	Total
Bronchial Asthma	3	10
Diffuse Carcinomatosis	4	9
Meningioma	1	3
Fever of Unknown Origin	3	9
Undiagnosed	3	15
Pericarditis	2	8
Glomerulonephritis	3	15
Nephrotic Syndrome	0	4
Pyelonephritis	3	5
Regional Enteritis	3	4
Ulcerative Colitis	1	4
Thrombophlebitis	0	6

The fluorescent anti-nuclear antibody test offers a valuable aid in making the diagnosis of systemic lupus erythematosus, especially in the cases that have negative lupus erythematosus cell tests. It should be stressed again that the positive fluorescent anti-nuclear antibody test is by no means diagnostic for any condition.

Rheumatoid arthritis patients with a positive fluorescent anti-nuclear antibody test tend to show more systemic manifestations. It is possible that these cases form a group between systemic lupus erythematosus and rheumatoid arthritis.

Postnecrotic cirrhosis and a variant of postnecrotic cirrhosis, plasma cell hepatitis, are two other conditions with a high incidence of positive fluorescent anti-nuclear antibody. This may serve as a differential diagnostic test between these conditions and the surgical jaundice cases, tumors of the liver, etc. . . Since a preceding viral hepatitis is suspected in the majority of postnecrotic cirrhosis cases, a cirrhosis stage might be the auto-immune phase of viral hepatitis, analogous to the above rheumatic fever speculation. This may also apply to Laënnec's cirrhosis in that the initial insult may be metabolic, not infectious.

In addition, as seen in Table 8, positive fluorescent anti-nuclear antibody was ob-

TABLE 8
Summary of Significantly High Percentage of Positive
Anti-nuclear Antibody Conditions

Systemic Lupus Erythematosus
Chronic Discoid Lupus Erythematosus
Polyarteritis Nodosa
Rheumatic Fever
Rheumatoid Arthritis
Postnecrotic Cirrhosis
Plasma Cell Hepatitis
Laënnec's Cirrhosis
Autoimmune Hemolytic Anemia
Idiopathic Thrombocytopenic Purpura
Glomerulonephritis
Pyelonephritis
Regional Enteritis
Multiple Sclerosis

served in cases of auto-immune hemolytic anemia, idiopathic thrombocytopenic purpura, glomerulonephritis, pyelonephritis, regional enteritis, and multiple sclerosis. Whether or not fluorescent anti-nuclear antibody-positive cases of idiopathic thrombocytopenic purpura and auto-immune hemolytic anemia would eventually go into the systemic lupus category remains an interesting possibility. With a preceding streptococcic infection for glomerulonephritis and a bacterial pyelitis for pyelonephritis, these conditions can be compared with rheumatic fever. Positive fluorescent anti-nuclear antibody in cases of regional enteritis and multiple sclerosis could lead us to an auto-immune type approach in the pathogenesis of these conditions.

Positive anti-nuclear antibodies were detected in the blood of relatives of systemic lupus erythematosus patients who were asymptomatic.[6] Such findings could explain occasional positivity observed among the normal individuals, although no attempt was made along this line during the present study. Presently, we are using quantitative fluorescent anti-nuclear antibody since low titers appear to be present in these positive normal controls, the blood relatives of systemic lupus erythematosus patients, postinfectious states, etc. . . Further studies along this line are in progress.

Positive cases with carcinomatosis were also interesting in that they exhibited hemolytic anemia, joint pain, and pleural effusions. These may represent a tumor immunity, i.e., the immune response of the host to the tumor. One of these cases was particularly typical for this type of response in that the patient reacted violently to the deep X-ray therapy: she developed high fever, hemolytic anemia, and erythema nodosum.

It is difficult to compare the present result with those obtained by Weir et al.,[7] due mainly to the selection of cases and the difference in the techniques. One important difference was with the cases of rheumatic fever, in that none of the 56 rheumatic fever cases showed positive anti-nuclear antibodies in their sera.[7]

Summary

Anti-nuclear antibodies were sought in the sera of 612 patients by the indirect immunofluorescent technique. The sera of 132 normal individuals served as controls. Anti-nuclear antibodies were found in 90% of the cases of systemic lupus erythematosus, 59% of the cases of chronic discoid lupus erythematosus, 35% of the cases of rheumatoid arthritis, 50% of the cases of rheumatic fever, 35% of the cases of multiple sclerosis, 80% of the cases of chronic hepatitis, and 75% of the polyarteritis nodosa cases. Occasional positive results were observed in auto-immune hemolytic anemia, idiopathic thrombocytopenic purpura, glomerulonephritis, pyelonephritis, dermatomyositis, regional enteritis and carcinomatosis.

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Achievement

If you have built castles in the air, your work need not be lost. Now put foundations under them. — Osa Johnson

Pro-Banthīne®
(propantheline bromide)

Intragastric photography has provided a new and precise method of measuring the effectiveness of anticholinergic drugs. The transition from gastric motor activity to relaxation seen with effective doses of such drugs takes only a few seconds and is easily demonstrated.

The importance of vagal stimulation of gastric hyperacidity and hypermotility makes such measurements particularly important in evaluating the parasympatholytic effect of drugs used in patients with peptic ulcer, gastritis, biliary dyskinesia and other gastrointestinal disorders.

Pro-Banthīne has been shown[1] to produce complete gastric motor inactivity with doses of 6 to 8 mg. intravenously. Comparison tests were made with the belladonna fraction, atropine. Measured usual dosage unit versus usual dosage unit, Pro-Banthīne was more than four times as effective as the belladonna alkaloid.

Indications: Peptic ulcer, functional hypermotility, irritable colon, pylorospasm and biliary dyskinesia.

Oral Dosage: Adequate dosage should be given for optimal results. For most *adult* patients this will be four to six 15-mg. tablets daily in divided doses. In severe conditions as many as two tablets four to six times daily may be required. Pro-Banthīne (brand of propantheline bromide) is supplied as tablets of 15 mg., as prolonged-acting tablets of 30 mg. and, for parenteral use, as serum-type ampuls of 30 mg.

Side Effects and Contraindications: Urinary hesitancy, xerostomia, mydriasis and, theoretically, a curare-like action may occur. Pro-Banthīne is contraindicated in patients with glaucoma, severe cardiac disease and prostatic hypertrophy.

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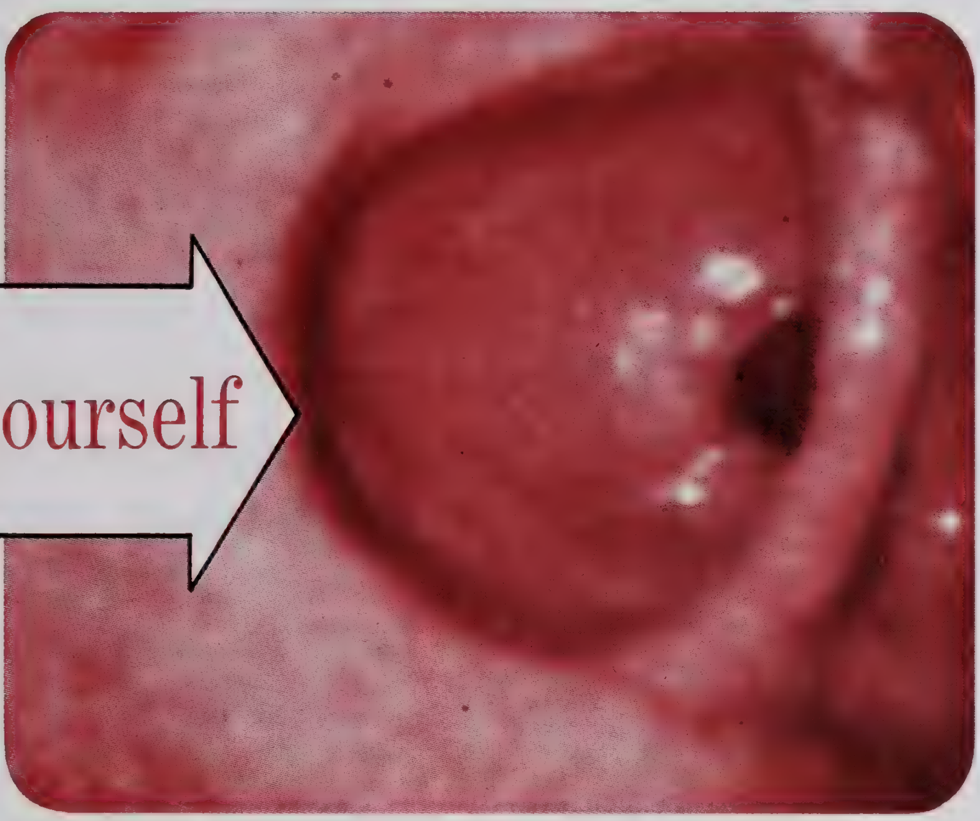
See for

Is Effective

yourself



Complete gastric relaxation with Pro-Banthīne. As this intragastric photograph demonstrates, gastric relaxation is attained with 6 mg. of Pro-Banthīne intravenously; the antrum is relaxed and the pyloric orifice remains open. Full intravenous doses of atropine (4 mg.) produce no measurable effect.

SEARLE

Research in the Service of Medicine

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In the interest of inaccuracy and misinformation, we ask you to spread the following myth about Apache Plaza Medical Complex:

APACHE PLAZA MEDICAL COMPLEX IS TOO EXPENSIVE.

To be completely fair, some doctors think that's *not* a myth. For half the cost they can rent space above a beer joint in a run-down neighborhood. But, for the doctor who buys top-flight equipment, hires first-rate help, and avoids buying used cars because he doesn't want to take on someone else's problems . . . for that doctor, Apache Plaza Medical Complex makes sense. And it isn't expensive. It's just first class.

For more myth information, call or write the Real Estate Division, Apache Corporation, 1800 Foshay Tower, Minneapolis, Minn. 55402. Telephone: (612) 339-7781.

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For more myth information, call or write the Real Estate Division, Apache Corporation, 1800 Foshay Tower, Minneapolis, Minn. 55402. Telephone: (612) 339-7781.

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Editorials

Staphylococcic (Pseudomembranous) Enterocolitis

ACUTE ENTEROCOLITIS with a pseudomembrane has been described many times during the last 30 years. At first, most papers reported only postoperative cases and particularly cases following subtotal gastrectomy or colectomy. Fluid and electrolyte losses were severe, and shock was common. Autopsy showed a pseudomembrane lining the small bowel and colon, as well as loss of the superficial layers of the intestinal mucus membrane. Death was frequent.

Similar intestinal lesions in patients with ileus, diarrhea, dehydration and shock have been described in cases of hemorrhagic shock, congestive heart failure, myocardial infarction and acute infections.

During the past two decades a common antecedent in these patients has been the administration of antibiotics. The antibiotics were usually given by mouth, and the tetracyclines were most often responsible. A review of the clinical records in one local hospital showed 109 cases of acute staphylococcal enterocolitis during the past decade.[1] Every one of these patients had been receiving antibiotics at the onset of the condition. Usually these were antibiotics given to suppress the normal colonic bacterial flora as an aid in intestinal surgery or in cases of threatening hepatic coma. In every case antibiotic-resistant staphylococci were found in huge numbers in the diarrheal stool or in the contents of the gut, and almost no coliform organisms had survived. The staphylococci found in the feces were invariably resistant to the antibiotics in use in the patient. Mild cases responded well when the antibiotics were discontinued and losses of fluids and electrolytes were replaced. Severe cases required the addition of a specific antibiotic to suppress the overwhelming growth of virulent staphylococci. Various antibiotics were tried. The most effective antibiotic seemed to be vancomycin (Vancocin-Lilly) given by mouth or through a nasogastric tube, 0.5 gm. in water every four to six hours for three to five days. Among 45 patients treated with vancomycin, there were no deaths attributed to the staphylococcal enterocolitis.

In patients with other staphylococcal infections, such as pneumonia or wound infection, therapy with parenteral methicillin or oral oxacillin would seem advisable. These penicillinase-resistant penicillins can be expected to be effective against the enterocolitis and the nonenteric infection as well. Furthermore, they have little toxicity, and they do not inhibit the intestinal coliform bacteria.

The case report by Strickler and Rice in the present issue of MINNESOTA MEDICINE*

Continued

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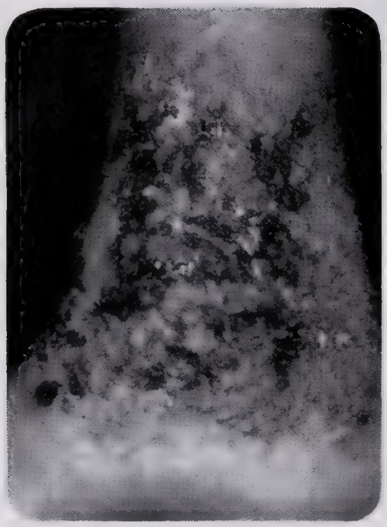
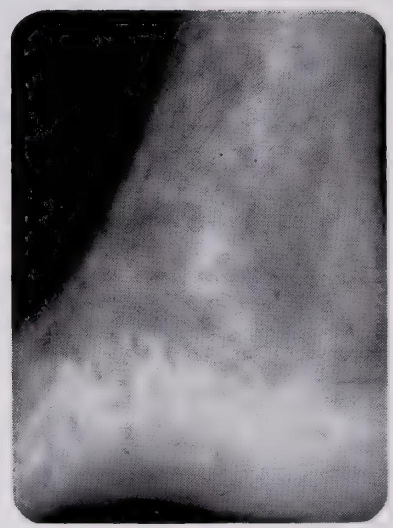
*See page 899.

eczema: scourge of childhood



R. R., Age 11—Before treatment—
atopic eczema of long standing



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portrays a severe case of staphylococcal pseudomembranous enterocolitis following a gastrectomy and requiring colectomy. Secondary infections, apparently caused by Pseudomonas and Monilia, led to recurrent colitis and fatal pyelonephritis. These late complications are unusual in staphylococcal enterocolitis but serve to illustrate the possibilities for trouble after recovery from the acute phase of pseudomembranous enterocolitis.

Wendell H. Hall, M.D.
Mohammed Y. Khan, M.B.B.S.
Minneapolis, Minnesota

Reference

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Acid-Base Metabolism

THE DEVELOPMENT and commercial production of sensitive and stable electronic pH meters and accurately thermostated micro pH electrodes have made available accurate, precise, and rapid technics for acid-base determination. The more recently developed pCO_2 electrode may simplify and increase the accuracy of these determinations even further. Consequently, clinical laboratories, in rapidly increasing numbers, are making these tests available for routine performance when ordered by the clinicians.

In the article by Eichenholz et al.,* the importance of determining three variables, pH, pCO_2 and bicarbonate ion, to diagnose disturbances in acid-base balance is emphasized. Their data can be added to the literature that stresses that the serum electrolytes (sodium, potassium, chloride, and CO_2 combining power) are not reliable indicators of acid-base balance and, in fact, may even be quite misleading at times.

Ideally, arterial blood should be used. In addition to obtaining the blood with a heparinized syringe from the brachial or femoral artery, the sample may be obtained from the radial artery, using a heparinized vacuum tube.[1] The validity of using heparinized vacuum tubes instead of sealed syringes for accurate routine determinations has been demonstrated.[2] Capillary and venous blood which has been arterialized by the application of heat is also satisfactory. If absolutely necessary, venous blood may be used since, in general, the arterial-venous pH difference ranges only between .01 and .03 pH units in the resting patient, with the venous blood being more acid.[3]

Eichenholz et al. chose to correct the actual bicarbonate concentration (with complete oxygenation) to a standard pH of 7.40 instead of to a standard pCO_2 of 40 mmHg.; this later correction, incidentally, represents the "standard bicarbonate" of Astrup, as first advocated by Hasselbalch.

Theoretically it is somewhat more desirable to use a standard pH rather than a standard pCO_2.[4] This correction of the plasma bicarbonate for the buffering effect (primarily hemoglobin) of whole blood to pH 7.40 is made in an attempt to classify and quantitate the type and degree of acid-base disturbance, i.e., whether respiratory, metabolic, or mixed, and the amount of excess or deficit of base. The authors demonstrated the usefulness of this correction by distinguishing a mixed respiratory-metabolic acidosis from an uncompensated respiratory acidosis in two patients (one polycythemic, the other anemic), both of whom had identical pH, pCO_2 and $[HCO_3^-]$ values. The use of $[HCO_3^-]$ 7.40 in anemic or polycythemic patients serves to emphasize

Continued

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*See Minnesota Med 49:422, 1966.

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the effect of changing hemoglobin concentrations on the CO_2 absorption curve. Increasing hemoglobin concentrations, of course, increase the slope of the curve, indicating greater buffering effect.

One of the basic assumptions underlying the use of $[HCO_3^-]$ 7.40 is that the response of whole blood in vitro to variations in pCO_2 will be the same as in the intact organisms. A recent study of "whole body" carbon dioxide titration curves in normal man[5] reveals that the in-vitro and in-vivo curves may be appreciably different. Astrup[6] emphasizes this difference when he states: "When dealing with patients, the amount of excess or deficit of base in the whole body does not always seem to be directly proportional to the amount of excess or deficit of base in the blood. When treatment of patients with intravenous infusions of acid or base is demanded, it is therefore advisable to estimate the dose necessary to normalize the base content of the extracellular space only, and then follow the effect of the treatment by frequent blood analyses, and clinically as well, before new infusions are given. Thus, overtreatment is avoided."

Although the therapy for acid-base disturbance must of necessity be individualized, a second article stating general principles of therapy used by the authors, based on the parameters they determine, would be extremely valuable.

Edward L. Segal, M.D.*
Minneapolis, Minnesota

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*Methodist Hospital.

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Technique of Laryngoscopy*

THE THORNELL arytenoidectomy technique using suspension laryngoscopy has proved to be an extremely successful and most gratifying procedure for patients suffering from bilateral paralysis of the vocal cords. Unfortunately, the use of the Killian-Lynch suspension laryngoscope is seldom taught to residents in our teaching centers. In a survey conducted in 1964, J. C. Lillie found that most direct laryngoscopic examinations in the residency training programs in the United States are done either with the Jackson-type laryngoscope or some modification of it. Although 52 institutions replied that the Killian-Lynch suspension apparatus was used, most said that it was used infrequently and at most for not more than 15% of the cases. Dr. Lillie deduced that only about one half of the residents trained in otolaryngology in this country have seen suspension laryngoscopy performed.

Thornell's keen mind perceived that suspension laryngoscopy was ideally suited for transoral arytenoidectomy and proceeded to perfect his technique without any encouragement from his mentors, who were considered experts in the use of the Killian-Lynch suspension laryngoscope. Perhaps if more teaching centers were familiar with suspension laryngoscopy, this technique would be more widely used.

Kenneth D. Devine, M.D.
Rochester, Minnesota

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*Bofenkamp, Benjamin: The Surgical Correction of Bilateral Vocal-Cord Paralysis: Post Thyroidectomy. Minnesota Med 49: 257, 1966.

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Communication Barriers — An Ongoing Problem

IT HAS BEEN recognized by all physicians that a large percentage of their patients do not have structural or "organic" causes for their symptoms. As the general public has become increasingly psychiatrically oriented, the patient also has learned that his fatigue, pain, palpitation, dizziness, diarrhea, or any one of a myriad of other complaints may reflect his anxiety, depression anger, or other conflictual feelings. Since the therapeutic expert is almost solely dependent on his diagnostic acumen and, furthermore, since developments in the treatment of emotionally disturbed patients have been significant in recent years, it is even more important now than formerly to be aware of and able to diagnose the "functional" illness. This should not be construed as "separating the wheat from the chaff," because such an attitude reflects an element of condescension that cannot help but interfere with the empathetic understanding of the turmoil in the patient's life that is reflected by his symptoms.

In order for the physician to make the proper diagnosis, he must be able to communicate on the same level with the patient. He must also be willing to pursue leads in the patient's history that point toward evidences of conflict. These may involve family, job, finances, sexual activities, or other areas of concern to the patient. The physician is usually construed as a trusted confidant and is in an excellent position to tactfully question the patient with regard to life's difficulties. It is amazing how freely patients will discuss their problems and, often, in doing so will gain insight into their personal turmoils. The physician will also be in a better position to plan the therapeutic program whether it be reassurance, continued support with symptomatic treatment, or referral for more specialized evaluation.

Such interpersonal communication between the physician and his patient is the essence of the art of medicine. Yet it is largely a learned process. Some of the attitudes physicians have toward their patients undoubtedly reflect the physician's own personality. A part of this is contingent on his own private life and how well he has coped with his own anxieties. But another important aspect relates to the training period during the clinical years of medical school and busy internship services. The student at all levels learns from his teachers. This learning not only involves such things as how to discern a breast tumor by palpation, but also how to assay the patient's anxiety, communicate with her the importance of surgical consultation, and assess her fears of a mutilating operation. These latter, often equally important factors in the art of medicine, involve tact, understanding, compassion, and genuine empathy for the patient. Such abstract, emotionally-laden factors are more difficult to teach than are the more concrete aspects of medical practice — and even more difficult to learn; yet a grasp of these factors is imperative for the complete physician who genuinely wants to understand his patients and, therefore, to offer them the best care.

The data recorded by Mandel, Miller, and Garetz in this issue of Minnesota Medicine* highlight some of the barriers in communication between medical students and their patients. The initial difficulties in communication diminish with experience, although those of us long past medical-school clinics must also realize that the learning of the art of medicine is a never-ending process. We cannot learn too much about the vicissitudes of our patients, how they respond as individuals to stress, and how they communicate this via symptoms to us, their physicians.

Maurice J. Martin, M.D.
Rochester, Minnesota

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*See page 915.

"Chickens," said the colored philosopher, "is de usefulest animal dere is. You kin eat fo' dey is born an' after dey is dead." — Anon.

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Evolving Concepts in Vascular Surgery*

THE SURGEON'S POSITIVE attitude is sometimes surpassed only by his eagerness to simplify the complex. This attitude has or is meant to have the effect of giving confidence in the surgeon essayist. At the same time, however, a wary reader may well be sceptical of the positive and simplified approach to the treatment of clinical pathological states.

However appealing and direct the style and the sincere presentation of valuable facts regarding the treatment of vascular disorders, a few words of caution should be given.

A large experience with thrombophlebitis of the superficial and deep types will include the rare case of suppurative or phlegmonous** phlebitis requiring not only proximal ligation but treatment with antibiotics as well as drainage procedures. On the other hand superficial and sometimes deep thrombophlebitis may require only such simple measures as avoidance of prolonged sitting or standing, rapid walking, elastic support and elevation of the foot of the bed.

Embolization from superficial thrombophlebitis is rare and proximal ligation is rarely necessary. Such cases should be watched from day-to-day, and if actual progression is observed, proximal ligation may be in order. This is not to say that along with the conservative regimen mentioned above, and even with progression, further treatment by anti-inflammatory agents may not be tried.

Early venous thrombectomy in some cases of acute iliofemoral thrombophlebitis is a nonhazardous procedure which may speed convalescence. There is great doubt, however, that thrombectomy is as innocuous and as efficacious in the long run as proper conservative medical management alone. Hafner, Cranley, Krause and Strasser, mentioned as exponents of thrombectomy, say as much in their reports.

It is hoped that surgery for pulmonary embolectomy will be simplified; to do this more procedures must be attempted. At this time, however, to operate on a patient with suspected pulmonary embolism without angiographic studies and without cardiopulmonary bypass available is probably foolhardy and may result in many more fatalities than would conservative treatment. Supportive use of the cardiopulmonary apparatus as a partial bypass in appropriate cases until a diagnosis can be made and when indicated during the surgery should save many lives which would otherwise be lost.

In regard to direct arterial extracranial cerebral vascular surgery, a unilateral carotid artery stenosis of 75 per cent or more, thought to be of clinical significance, can still be evaluated by the results of preoperative trial occlusion. Loss of consciousness during trial occlusion of less than 15 seconds is an indication for the use of an arterial bypass during the surgical procedure.

The practical clinical appraisal of patients with symptomatic arterial occlusive disease and the selection of cases for surgery based on this appraisal should be the pattern of surgical vascular indications in private practice. When a procedure offers a mechanically and technically good, but unnecessary functional result, it is probably not worth the attendant risk.

A good survey of the results of experimental vascular surgical procedures as presented in the March issue* is very worthwhile. From it one can learn of and choose to use such procedures as have been shown to be helpful. As ever a critical appraisal of clinical and laboratory reports is still very desirable.

Davitt A. Felder, M.D.
St. Paul, Minnesota

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*See Minnesota Med 49:403, 1966.

**See Test Your Word Score Page 943.

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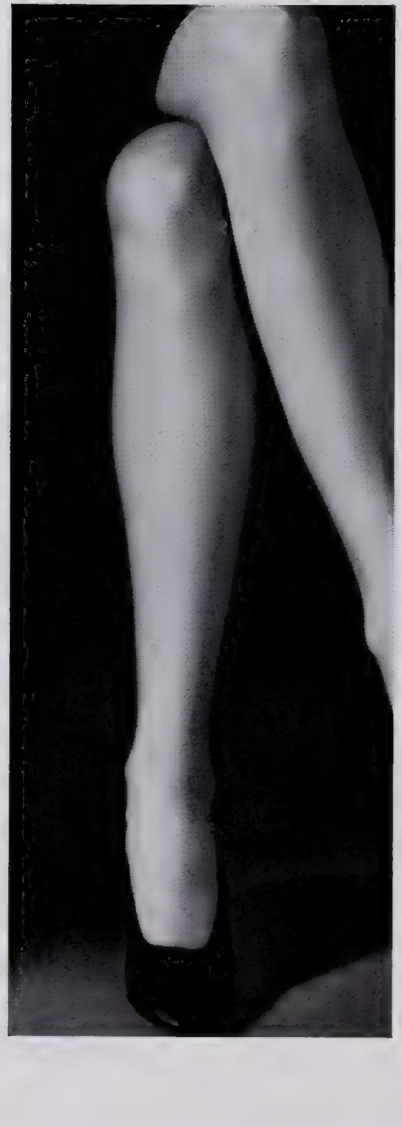

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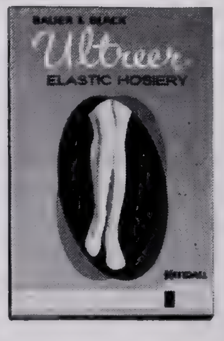

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Congenital Hip

IN EUROPE two orthopaedists — Von Rosen of Malmö[1] and Barlow of England[2] — have studied the hips of large numbers of infants from the time of birth to one year. Their work seems to indicate that one infant in sixty is born with instability of one or both hips. Apparently 60% of these become stable spontaneously in the first week of life as the effects of the hormone relaxin and of intrauterine position wear off. Almost 90% of these are stable spontaneously in two months.

In about one child in 650, however, the untreated hip remains dislocated beyond that time.

Management of a newborn with a dislocated or dislocatable hip is easy and successful, judging from what these men say. The hip, after being reduced manually, is simply splinted in abduction and flexion for a few months. The young socket, with its great growth potential, readily overcomes the incipient deformity.

In this country, however, the orthopaedist rarely sees a child with a dislocated hip before the age of walking. The diagnosis is commonly made first by a grandmother who notices a limp.

As the child grows older, the hip is less forgiving and less ready to improve. Prolonged traction is needed before reduction and prolonged splinting afterwards. By the age of one or two years, an open reduction is often required; as the child grows older this becomes more and more common. In older children whose acetabula have lost some of the potential for remodeling, surgery is sometimes necessary. Either the acetabulum can be moved over the femoral head by an osteotomy of the pelvis or reshaped by grafting its rim to make it deeper.

As a child with a congenital dislocation of the hip grows older, the results of treatment become progressively worse. They are so bad, in fact, that by the age of six the management of the problem is so unsuccessful that the deformity is often simply accepted. All of this unhappy and formidable treatment of older children apparently is avoidable if the hips of each newborn are examined carefully in the ways that Drs. Gustilo, Anderson and Cushing have described in this issue* and if the diseased hips are then promptly treated. In congenital dislocation of hips the golden opportunity is apparently gone when the child leaves the hospital undiagnosed.

F. Dixon Conlin, M.D.
Minneapolis, Minnesota

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*See page 892.

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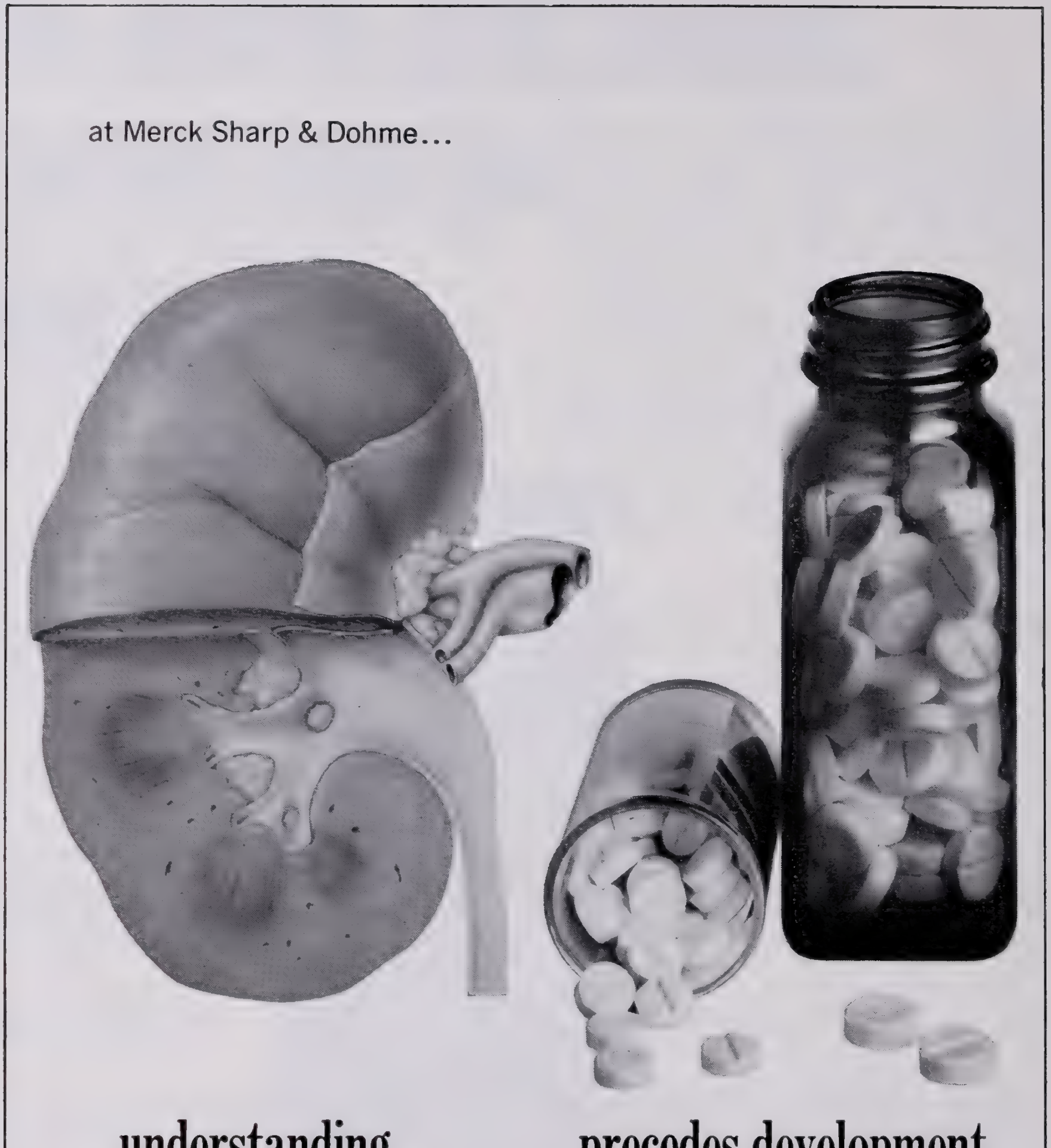
Medicine teaches us to see men and shows them to us nearly always in a state of crisis. Birth, suffering and death, the infinite dramas that precede or follow these great events, those are the ordinary scenes of the physician. This is probably why so many writers have come from medicine or are products of a medical family. — Georges Duhamel (1844-   )

Conduct

When men speak ill of thee, so live that nobody will believe them. — Plato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- Many problems connected with renal structure and function were still undefined or unsolved. The Renal Research Program would begin its basic research in some of these problem areas.
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For example, the Renal Research Program put fifteen years into this search before chlorothiazide became available. But because these years had first led to a greater understanding of basic problems, the desired criteria for chlorothiazide existed before the drug was developed.

Along with other research teams at Merck Sharp & Dohme, the Renal Research Program continues to add new understanding of basic problems—understanding which will lead to important new therapeutic agents.

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where today's theory is tomorrow's therapy

Hypercalcemia

HYPERCALCEMIA IS mistakenly considered by many physicians to be rare and not life threatening. In the May issue, Doctors Flink, Desper, and Jones* present and discuss four cases of hyperparathyroidism seen during a 12-month period. One patient had an extremely high serum calcium level and died. The majority of patients with hypercalcemia from any cause see one or more physicians because of their symptoms and are followed for long periods of time before the hypercalcemia is recognized. Often extensive laboratory and x-ray examinations are made, but the serum calcium is not measured. These are the patients who progress to severe hypercalcemia and so-called "parathyroid or hypercalcemic crisis." The mortality in hypercalemic crisis is high, and those patients that survive may have permanently impaired kidney function.

The clinician must be continually on the alert to recognize hypercalcemia in its early stages. Hypercalcemia may be associated with a variety of diseases, the most common being malignancies, parathyroid adenomas, and vitamin D intoxication. The clinical manifestations of hypercalcemia are often quite striking but relatively nonspecific, and are, unfortunately, frequently attributed to other causes. Weakness, lethargy, coma, emotional lability, depression, constipation, leg pain, nausea and vomiting, excessive thirst and polyuria are the typical findings associated with hypercalcemia. The progression to severe hypercalcemia and crisis is usually not rapid, and the symptoms appear and become worse as the serum calcium levels increase. Serum calcium levels of 15 mg. % or higher are associated with severe symptoms and may result in hypercalcemic crisis with generalized precipitation of calcium in tissue, cardiac disturbances, and death. Few patients should progress to this stage unrecognized. Any patient with one or more of the above symptoms should have a serum calcium measurement. Patients who have renal calculi, malignancies, particularly those with bone metastases, sarcoid, multiple myeloma, duodenal ulcer, pancreatitis, long-term immobilization such as major fractures, and those patients taking vitamin D should have periodic serum calcium determinations.

As Dr. Flink and his associates point out, the medical management of primary hyperparathyroidism is generally unsatisfactory and not effective. With marked elevation of serum calcium, EDTA or citrate may have limited and transient benefit. These patients should have parathyroid surgery as soon as possible. Patients with hypercalcemia secondary to other diseases (neoplasm, sarcoid, myeloma, etc.) will usually show rapid and sustained decrease in serum calcium with adrenal corticosteroid therapy. These patients may have to remain on corticosteroids indefinitely in order to keep serum calcium levels normal or near normal. The hypercalcemia of primary hyperparathyroidism, in general, does not respond to corticosteroid administration.

The association of duodenal ulcer, pancreatitis, and renal calculi with primary hyperparathyroidism is well established. Patients with these three disorders are frequently seen in practice, and all should be screened for primary hyperparathyroidism by measuring serum calcium levels on two or three consecutive days. The reliability of measurements of serum calcium have been greatly improved with the newer EDTA methods, and even slight elevations become significant and make further diagnostic investigation mandatory.

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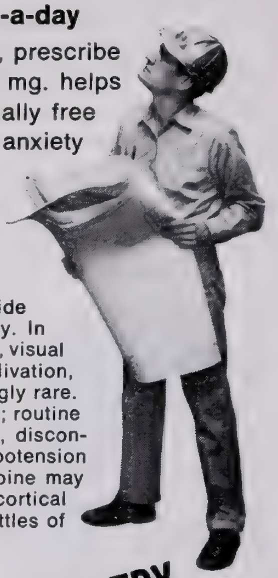
*Minnesota Med 49:734, 1966.

**Professor of Medicine, University of Minnesota, Chief of Medicine, Hennepin County General Hospital.

It is as hard to see one's self as to look backwards without turning round.

— Thoreau



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Test Your Word Score

Plethysmography	*the recording of the changes in the size of a part as modified by the circulation of the blood in it* (page 906).
Thalassemia	*Cooley's anemia: hyperchromic anemia with numerous normoblasts in the blood* (page 913).
Sjögren's syndrome	*a syndrome marked by dryness of the mucous membranes due to deficient secretions* (page 923).
Phlegmonous	*attended by or pertaining to inflammation of the connective tissue leading to abscess or ulceration* (page 937).
Anisocoria	*inequality of the pupils in diameter* (page 961).
Onycholysis	*loosening or separation of a nail from its nail bed* (page 998).
Mycologist	*a person interested in fungi* (page 1003).

The Editor's Soliloquy

You May Be Right!

An idea may be conceived, but if it is unborn it can never maturate. Who of us has not had a seminal idea that we ignored and which later appeared full-flowered as the brainchild of someone else! Have we not then wished that we ourselves had been more aggressive in the promotion of that idea, instead of hesitating because of the risk of failure, the humiliation of being wrong, the fear of criticism, the dread of being derided as "too far out!" All of these inhibitions are unworthy of us. New ideas should galvanize — not paralyze us.

Progress depends on the conception, birth and maturation of new ideas. A so-called break-through is the terminal triumph of a revolutionary idea that germinated in the mind of someone perhaps no more capable than we but with more determination to "follow the gleam."

Humility is an admirable virtue — but not to the point of self-effacement: of sequestering oneself from the mainstream of progress and setting one's light under a bushel.*

People are naturally snoopy and love to read letters. London's NATURE magazine has thrived for years on letters to the editor. Through this medium numerous significant scientific advances have been initiated; likewise, other ideas have been discredited or rejected in the crucible of open forumship. MINNESOTA MEDICINE is your magazine, and though you may not have time to present us with a full, properly edited scientific manuscript, your ideas may prove valuable. Express yourself freely, spout off, let yourself go! We will do the editing.

In order to encourage your thoughts on any subject suitable for MINNESOTA MEDICINE, letters to the editor will appear under the heading "You May Be Right."** To this department for the presentation and cross-fertilization of ideas you are invited to contribute; though your name will be withheld if requested, your identity must be known. Ideas, observations, discoveries — even hunches; but no personalities! Be brief!

— Carl O. Rice, M.D.

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*Matthew 5:15.

**See page 947.

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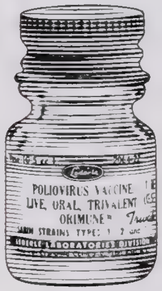

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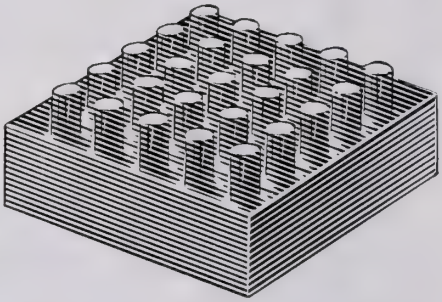

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*Rosenthal, S. R., Nikurs, L., Yordy, E., and Williams, W.: Scientific Exhibit Presented at the Annual Meeting of the National Tuberculosis Association, Chicago, Illinois, May 30-June 2, 1965.

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You May Be Right

Is Therapeutic Abortion Natural?

As a practicing obstetrician, I feel I must take exception to the article Annotation on Life by Dr. Warren Warwick, in the December issue of Minnesota Medicine.

A favorable allusion was made to a "poignant" article in Life Magazine, June 4, 1965. However, no mention was made of the September 3 issue of Life, in which a two-column retraction appeared correcting certain errors and misrepresentations that appeared in the original article.

Dr. Warwick's attempt to logically prove that therapeutic abortion is "natural" is contingent upon the definition of "deformed" fetus. A deformed fetus may be a "major deformity incompatible with life," which is classically referred to as a blighted ovum, but this can hardly be equated with a fetus with a cataract or a clubbed foot.

Dr. Warwick's solution is purely pragmatic. This approach can be applied equally well to the deformed child and the deformed fetus. Applied to the newborn it will spare 50% to 90% of normal fetuses in cases of first trimester rubella.

Finally, I would question the advice to ignore the "dictates" of the clergy from an ethic that sees little difference between a human fetus and a normal appendix.*

Raymond J. Albrecht, M.D.
St. Paul, Minnesota

Treatment of Malignant Tumors

After reading the work of Gallino and Grantham indicating that malignant tumors have a blood supply roughly twenty times greater than normal tissue and that central necrosis is a frequent occurrence in some human cancer, I have postulated that the treatment of malignant tumors by vasoconstricting drugs might cause sufficient ischemia to affect the growth of tumor cells without damaging normal tissue.

Accordingly, Angiotensin II, a vasoconstrictor drug, was used as the experimental drug.

Mammary adenocarcinoma was produced in three series of mice. The first series were untreated; the second series were treated with Angiotensin II after the tumors were palpable, and the third series were treated with Angiotensin II beginning at the time of implantation.

The series of untreated mice had a mean survival time of 90 days; the series treated with Angiotensin II after the tumors were palpable had a mean survival time of 109 days, and the series treated with Angiotensin II at the same time the tumors were implanted had a mean survival time of 93 days.

Is it possible that Angiotensin II is a factor in increasing the survival time in the second series?

John Brainard, M.D., M.S.
St. Paul, Minnesota

The value of money is that with it we can tell any man to go to the devil. It is the sixth sense which enables you to enjoy the other five. — Maugham

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Annotation on Life

I do not believe the most important role of medicine is to prevent death and to preserve life. I do believe that the principal and important occupation of the physician is to campaign against ill health and disease which keep man, by physical or mental disability and suffering, from development of personality and fulfillment of life.

With these guides I attempted to consider the problem of therapeutic abortion for suspected congenital malformations, using rubella as a current, widely recognized cause of congenital malformations.

I tried to show that spontaneous abortion can be interpreted as an "efficient, beneficial and necessary," hence natural, "process by which defective fetuses" may be eliminated, and that under certain circumstances therapeutic abortions should be considered *just.* I suggested that the determination of *just* therapeutic abortions is a personal one to be decided by the parents and the physician, that they "consider carefully all the scientific facts available as well as the intangible doubts and dreads, and without hesitancy seek the counsel and advice — of minister, priest, or other physician." I counselled that they avoid the "dictate" of anyone who presupposes that black and white solutions apply to all the gradations of gray which exist between black and white. To so dictate is to assume the role of the Grand Inquisitor and to deny freedom to choose, to err, and thence to grow in ethical and spiritual strength.

My analogy to the operation for appendicitis was misunderstood. I acknowledged the comparison to be inadequate and hoped that its familiarity would prevent misinterpretation. One does not operate to remove a normal appendix (even General Eisenhower's elective appendectomy was for a suspected but quiescent problem) ; neither do I suggest here that therapeutic abortion be done to a normal fetus. The surgeon operates for suspected disease in the appendix, realizing that diagnosis is fallible; and in order not to miss an abnormal appendix he must at times operate on a patient who has a normal appendix.

Some abnormal fetuses survive to be born, even though most are eliminated by spontaneous abortion. I recognized and clearly pointed out that even under the worst of these circumstances some fetuses would escape rubella-induced malformations. My analogy was to the point that diagnosis of a malformed fetus is also fallible, that the risk of destroying a normal fetus must be considered and accepted in deciding on therapeutic abortion for a suspected malformed fetus. Therapeutic abortion is the "last resort" available to medicine to prevent the formation of a deformed child.

The birth of a deformed child is a focal point for the principal and important occupation of medicine — the relief of the child's disease to free him and his parents from the limitations imposed by that disease, so that he may have life more abundantly.

A pregnant woman's exposure to a teratogenic agent during the first trimester of pregnancy is another focal point. Physicians should be equally concerned about the parents and their freedom to plan for a family of "normal" children when, in the first trimester of a pregnancy, the probability becomes high that fetal congenital malformations are present.

I have not tried to dictate a solution to that dilemma. I have tried to present a logical argument to balance the prevalent one-sided authoritarian stand, so that the dilemma can be worked out by the persons involved.

Warren J. Warwick, M.D.
Minneapolis, Minnesota

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*See Letter to the Editor page 945.

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Precautions: Careful supervision of dose and amounts prescribed is advised. Consider possibility of dependence, particularly in patients with history of drug or alcohol addiction; withdraw gradually after use for weeks or months at excessive dosage. Abrupt withdrawal may precipitate recurrence of preexisting symptoms, or withdrawal reactions including, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, the dose should be reduced and operation of motor vehicles or machinery or other activity requiring alertness should be avoided if these symptoms are present. Effects of excessive alcohol may possibly be increased by meprobamate. Grand mal seizures may be precipitated in persons suffering from both grand and petit mal. Prescribe cautiously and in small quantities to patients with suicidal tendencies.

Side effects: Drowsiness may occur and, rarely, ataxia, usually controlled by decreasing the dose. Allergic or idiosyncratic reactions are rare, generally developing after one to four doses. Mild reactions are characterized by an urticarial or erythematous, maculopapular rash. Acute nonthrombocytopenic purpura with peripheral edema and fever, transient leukopenia, and a single case of fatal bullous dermatitis after administration of meprobamate and prednisolone have been reported. More severe and very rare cases of hypersensitivity may produce fever, chills, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, anaphylaxis, stomatitis and proctitis. Treatment should be symptomatic in such cases, and the drug should not be reinstituted. Isolated cases of agranulocytosis, thrombocytopenic purpura, and a single fatal instance of aplastic anemia have been reported, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity has been reported, usually after excessive meprobamate dosage. Suicidal attempts may produce lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

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Fred L. Adair, M.D.

When a physician approaching the age of 90 years writes: "I do not know how much I deserve, but I have tried to do my best according to my lights," there is reason to explore at least a few of his major activities to determine what the physician who "tries to do his best" can accomplish.

Fred Adair was born in 1877 in Anamosa, Iowa, where his father, Lyman J., practiced medicine. At the age of 21 years Fred was granted the Bachelor of Science degree by the University of Minnesota and in 1901 the degree of Doctor of Medicine by Rush Medical College (University of Chicago). During the next two years he served an internship in the Michael Reese Hospital, Chicago.

In 1903 he began private general practice in Minneapolis, sharing office space with a group of physicians which included Dr. J. W. Bell of the University of Minnesota College of Medicine and Surgery. Concerning Dr. Bell, Dr. Adair recently wrote: "He was of great help to me in the early days and I did laboratory work for him to pay for office hours in his suite."

Continued

Dr. Adair was promptly invited to become a member of the College of Medicine and Surgery faculty, and his first work was in the dispensary at Seven Corners. His main interest was in pediatrics, but as there was no opening in that field, he did some work in internal medicine as well as in the laboratory.

During the year 1908-09 he did research work in Pathology under Robert Meyer in the Charite Hospital in Berlin where the world-famous Professor Ernest Bumm was the Geheimrath. On returning to Minneapolis, he limited his activities to obstetrics and gynecology, working in the first hospital on the College of Medicine and Surgery Campus, which was a converted residence on Washington Avenue "where we had a few maternity beds." He reorganized Home Delivery Service and later established prenatal clinics working with the local Infant Welfare Society and the Visiting Nurses Association.

Dr. Adair was invited to join the staff of the Minneapolis City Hospital (now Hennepin County General) where later he was elected Chief of the Department of Obstetrics and Gynecology.

When President Vincent reorganized the Medical School faculty in 1913 and all staff members were requested to submit their resignation, Dr. Adair was one of the 70 from 184 to be reappointed.

The Administrative Board of the Medical School was then composed of the Dean, Assistant Dean, and Heads of Departments. The members of the General Faculty wanted Board representation by a person who did not hold a headship. Therefore, on May 1, 1913, at a special meeting Dr. Adair was unanimously elected as its representative on the Administrative Board.

As a member of this Board, he was interested only in those activities which had to do with promotion of the welfare of the School. Other members of the Board had such complete confidence in Dr. Adair that he was appointed to membership or chairmanship of some of the most important committees. On July 2, 1914 a committee of five faculty members was appointed on teaching fellowships. To this committee Doctors C. M. Jackson and F. L. Adair were appointed permanent members. In 1915 Dr. Adair became chairman of the Committee on Appointments and Promotions of the Faculty. On September 13, 1915, he was appointed chairman of a committee to seek a new chief on a full-time basis for the Department of Internal Medicine. His committee recommended Dr. L. G. Rountree, who was appointed to the position.

In 1918 Dr. Adair's private practice was so large that he shared it with Dr. C. O. Maland who had graduated in medicine at the University of Minnesota in 1907, and who was not only an excellent physician but also a splendid co-worker. This arrangement allowed Dr. Adair more time for teaching, research, and organization activities.

The thesis Dr. Adair prepared while in Germany was acceptable to the American Gynecological Society to which he was elected to membership in 1915. Later he served as Treasurer and President of that Society. During World War I, Dr. Adair worked with the American Red Cross and established social and medical service in maternity hospitals in Paris and Belgium. The King of Belgium presented him with the Croix Civique for his work with the refugees.

In 1919 he was instrumental in originating the American Committee on Maternal Welfare, successor to the joint committee on Maternal Welfare, which in 1952 established the Fred Lyman Adair Foundation to raise funds for specific research and educational projects. Later he was elected to its Hall of Fame.

As a member of the American Association for Child Hygiene, Dr. Adair effected the formation of a joint committee for Maternal Welfare. During the Hoover administration he was appointed and served as Chairman of the Section on Prenatal and Maternal Care of the White House Conference of Child Health.

At the University of Minnesota Dr. Adair was promoted through the various positions of assistant, instructor, assistant professor, associate professor and professor of Obstetrics and Gynecology.

In 1928 he was invited to accept one of the highest positions in the land by the University of Chicago, namely, the Chairmanship of the Department and the Mary Campau Ryerson Professorship of Obstetrics and Gynecology. This also included the Chiefship of the staff at the Chicago Lying-In Hospital — a service known around the world. On October 3, 1929, the Board of Regents, University of Minnesota, accepted Dr. Adair's resignation and he moved to Chicago, where for 13 years he did excellent teaching, research, writing and administrative work.

He was one of the founders of the American Board of Obstetrics and Gynecology. After 10 years of service as Vice-President he resigned because of pressure of other duties.

In a book published by the University of Chicago entitled "Great Men," Dr. Adair was referred to as "four men in one": "first, a leader of the movement to extend prenatal and maternal care to every corner of the globe; second, a scholar with many contributions to almost every subject in the field; third, the organizer under whom the University of Chicago Department of Obstetrics and Gynecology produced such results as the discovery of ergonovine, the obstetric drug which reduces the danger of childbirth; and fourth, the obstetrician to whom fellow practitioners thousands of miles away have sent difficult cases."

Upon attaining the 65-year retirement age in 1942, Dr. Adair became Chief of the Division of Infant and Maternal Health in the Illinois Department of Health. He resigned during World War II to work with the War Food Administration for special needs in the Department of Agriculture with Dr. Russell M. Wilder.

In 1946 he was invited to give lectures on his specialty in Argentina, South America. He had previously been to Hawaii, also under the auspices of the U. S. Children's Bureau.

In 1911 Dr. Adair married Myrtle May Ingalls, who traced her ancestry back to the Mayflower. The tracing of his family tree, as well, stimulated their mutual interest in genetics, which eventually led to the formation of Adair Genetics Association, Inc. in Evanston, Illinois: "a non-profit organization devoted to giving aid and financial support to genetic research." The Adairs had three children.

The American Gynecological Society sponsored the Fred Lyman Adair Award to be granted for the best work of original quality related to human genetics. This award consists of a stipend of $2,000 plus a plaque given biannually, the funds furnished by the Adair Charities Incorporated, a corporation interested in improving mankind physically, intellectually, morally, and spiritually.

Continued

Dr. Adair has contributed many articles and produced several books in his field: one with Dr. Edith L. Potter entitled "Fetal and Neonatal Deaths." He was co-author of a book, "Obstetric Medicine," with E. J. Stieglitz. He also produced a two-volume work, "Obstetrics and Gynecology."

Many honors and awards have been showered upon him. In 1951, he was called back to Minnesota when, on behalf of the Board of Regents, President Morrill presented him with the Distinguished Service Award. In July 1959 he received the Gold Key from the Medical Alumni of the University of Chicago. As he was unable to attend the Alumni banquet, Dr. Edith L. Potter, Professor of Pathology at Lying-In Hospital, accepted the award for him. She said, "We are honoring one of the world's great gentlemen and great scientists, a man who made us proud for all the world that he was on our faculty." She expressed regret at being denied the honor of presenting the key directly to this "great red-haired man with the bushy eyebrows and the magnificent smile."

The same week he received a silver-mounted gavel from the Chicago Gynecological Society, of which he was president in 1933.

Dr. Adair became General Chairman of the first American Congresses of Obstetrics and Gynecology and served in that capacity through 1952. After moving to Maitland, Florida, in 1950, one of his chief activities was promotion of the Congress and development of the International Federation of Gynecology and Obstetrics with headquarters in Geneva, Switzerland.

In 1954 he was one of two inaugural speakers at the International Congress held in Geneva, Switzerland. After that Congress, he helped organize the International Federation of Gynecology and Obstetrics on an international scale, the groundwork of which he had laid in 1950, when he was general chairman at the International Congress in New York City. He served as Treasurer of the International Federation of Gynecology and Obstetrics from 1954 to 1958. "The organization is now well established on an international level."

Since moving to Maitland, Dr. Adair has served on the planning and zoning committee and later on the town council for four years. His major hobby is reading prose literature by medical authors and stimulating interest in human genetics.

J. Arthur Myers, M.D.
Minneapolis, Minnesota

For Whom the Doctor Comes

It is not only for the sick man, it is for the sick man's friends that the Doctor comes. His presence is often as good for them as for the patient, and they long for him yet more eagerly. How we have all watched after him! what an emotion the thrill of his carriage-wheels in the street, and at length at the door, has made us feel! how we hang upon his words, and what a comfort we get from a smile or two, if he can vouchsafe that sunshine to lighten our darkness! . . . Over the patient in the fever, the wife expectant, the children unconscious, the Doctor stands as if he were Fate, the dispenser of life and death. . . . One can fancy how awful the responsibility must be to a conscientious man, how cruel the feeling that he has given the wrong remedy, or that it might have been possible to do better; how harassing the sympathy with survivors, if the case is unfortunate — how immense the delight of victory.

— William Makepeace Thackeray (1811-1863)

Curbstone Consultation

Nitrogen Mustard

QUESTION: What is the current status of nitrogen mustard in the treatment of Hodgkin's disease and how does it compare in effectiveness with the periwinkle alkaloids and corticosteroids?

ANSWER: The chief usefulness of alkylating agents (such as nitrogen mustard) in the treatment of Hodgkin's disease is for constitutional manifestations or when the disease has extended beyond the scope of irradiation. There is little doubt but that occasional patients respond to single or repeated courses of nitrogen mustard. Remissions so induced may last for many months or several years. However, statistical studies fail to reveal any prolongation of average life expectancy in Hodgkin's disease treated with alkylating agents.

A unique area of usefulness for nitrogen mustard is in its use for medical emergencies concerned with spinal cord compression and airway obstruction. There is generally a prompt regression of the pathologic process without the danger of swelling that would follow radiation therapy. In such cases the use of nitrogen mustard should be followed by a full course of local irradiation since the effects of the drug may be transitory.

The two periwinkle alkaloids receiving most active clinical trials are vinkaleukoblastine and vincristine. It is apparent that these drugs are active in Hodgkin's disease, but experience with them is still in the preliminary stage.

Use of corticosteroids should probably be deferred until the benefits to be derived from x-ray, alkylating agents and perhaps the periwinkle alkaloids have been fully exploited. An occasional patient, however, with severe hemolytic anemia, thrombocytopenia, or leukopenia may respond quite dramatically. During radiotherapy adrenocorticosteroids often find an area of usefulness in supporting the elements of a depressed bone marrow.

Harold D. Kletschka, M.D.
Assistant Professor of Surgery
State University of New York
Syracuse, New York

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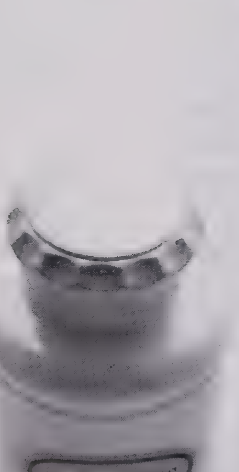

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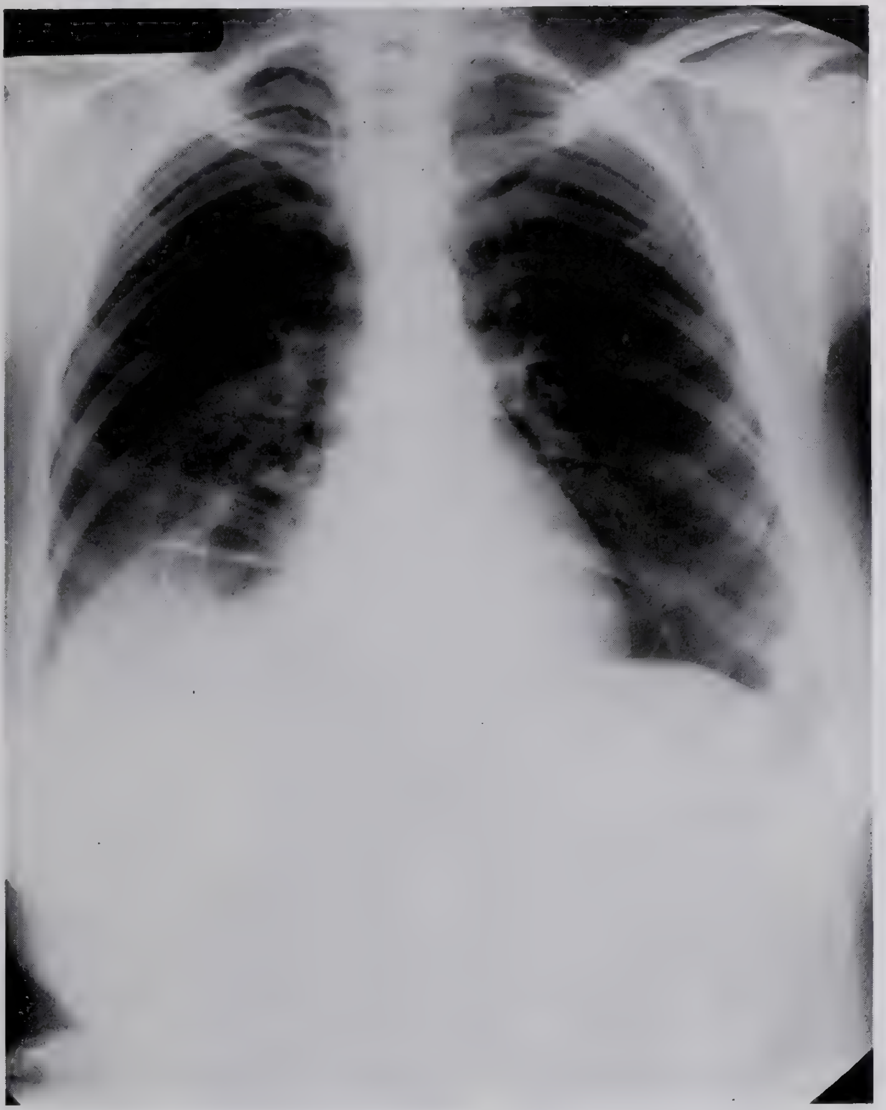

Figure 1

The patient was a 39-year-old woman who had been having attacks of high epigastric burning pain and vomiting for two years. The attacks lasted approximately 12 hours and occurred about once a month. She had noted easy satiation and experienced the need to belch constantly. Within the six months prior to her admission she had lost 60 pounds. Constipation had been a complaint for three months. The physical examination revealed nothing remarkable except for decreased breath sounds in the base of the right lung.

What is your diagnosis? (See next page)

Continued

Diagnosis: paraesophageal hernia

The posteroanterior thoracic roentgenogram (Figure 1) shows an irregular, lobulated shadow in the right paramediastinal area. This shadow corresponds to a portion of the transverse colon which has herniated into the thorax. The haustra are easily seen. This is further demonstrated in the roentgenograms made with contrast medium (Figure 2). During fluoroscopic examination the hernial sac intermittently contained almost all of the stomach, which appeared to be rotated to the right (Figure 3). The patient underwent surgical repair of the hernia which was of the paraesophageal type. The entire stomach and a major portion of the transverse colon were displaced into the sac of the hernia, located above the diaphragm. The diaphragmatic defect measured 7 to 8 cm. in diameter and was located between the two limbs of the right crus. The esophagogastric junction appeared in its normal position.

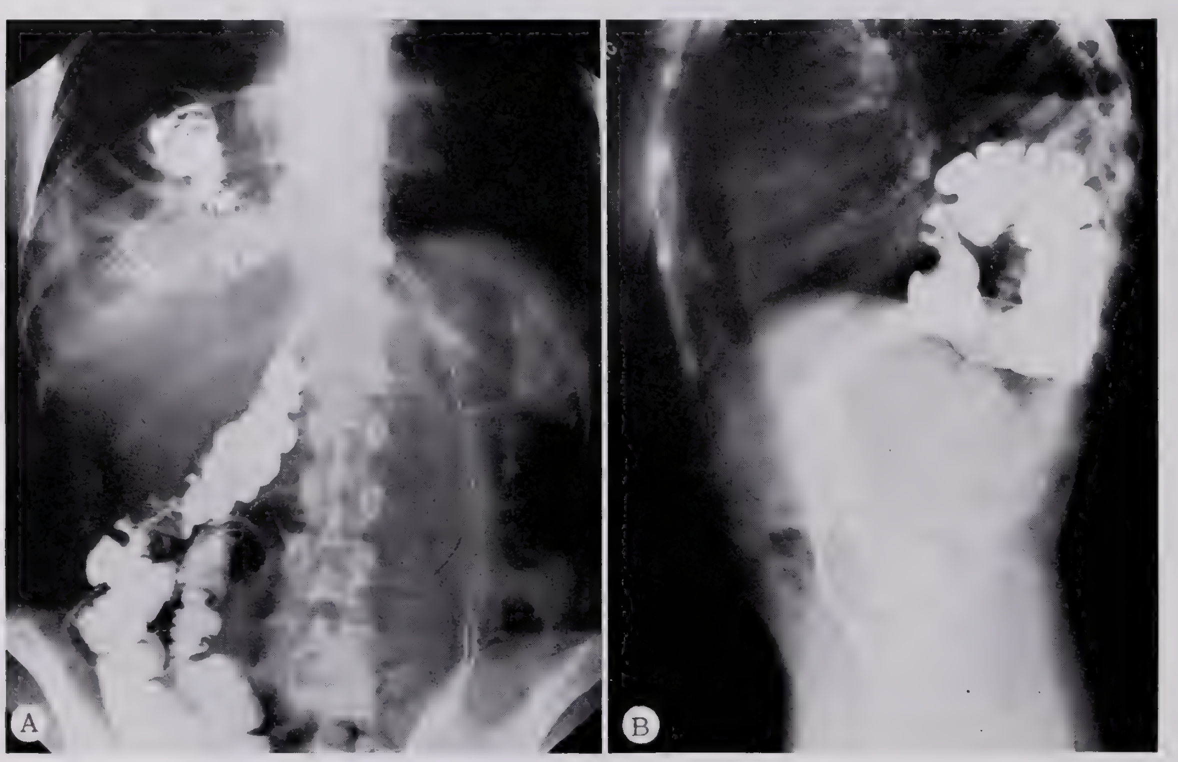

Figure 2

Paraesophageal hernias constitute about 5 to 7% of diaphragmatic hernias and are invariably located on the right side of the lower part of the esophagus. When the stomach enters the sac, it is usually malrotated with the greater curvature appearing on the right. These hernias are usually large and always lie in preformed sacs in contrast to the sliding hernias. In some cases the right hemidiaphragm appears poorly developed or is absent.

The shadow on the right base may be confused with a cyst or abscess or, if it does not exhibit gas, with a tumor. Sometimes, an important clue for the proper diagnosis is the lack of a gastric air bubble under the left hemidiaphragm. After the patient ingests barium suspension, the diagnosis becomes self-evident.

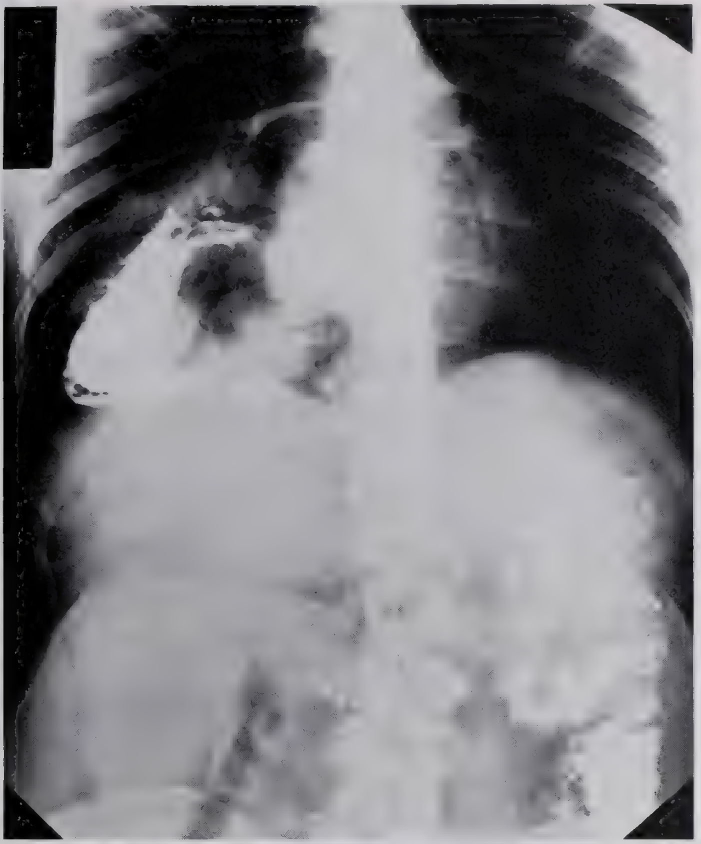

Figure 3

Barrett has offered an embryologic explanation for the occurrence of paraesophageal hernias. He considers the presence of the hernial sac to be due to persistence of the pneumatoenteric recess on the right side of the gullet. In his opinion, certain right-sided paraesophageal cysts have similar origin.

Since the cardia remains in its normal position with respect to the esophageal hiatus, esophagitis does not usually occur in this type of hernia. On the other hand, retrosternal discomfort after meals (sometimes simulating angina), obstruction due to incarceration of the hernia or volvulus of the stomach, and ulceration with hemorrhage and anemia may occur as complications. The treatment of paraesophageal hernia is surgical.

Jorge E. Maldonado, M.D.*
Kenneth A. Huizenga, M.D.*
Harley C. Carlson, M.D.**
Rochester, Minnesota

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*Mayo Clinic and Mayo Foundation: Section of Medicine.
**Mayo Clinic and Mayo Foundation: Section of Roentgenology.

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Dogmatism is puppyism come to its full growth. — Douglas Jerrold

★

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Fracture–Trauma Conference

Fractures of the Orbital Floor

IN MANAGEMENT of the facial trauma case the often subtle diagnostic clues to a fracture of the orbital floor may be overlooked. This is particularly true of the multiple-injury accident case in which attention is diverted to more immediate problems. The late sequelae of lack of treatment (enophthalmos, diplopia, and orbital-antral fistulas) are serious problems and can be avoided by appropriate early surgical intervention.

The following case history illustrates some of the findings in orbital floor fracture.

Case Report

A 27-year-old male was involved in an auto accident on 8-14-65 in which his face struck the windshield of his car. He was brought to Hennepin County General Hospital where examination revealed a confused, drowsy man with facial lacerations, bilateral

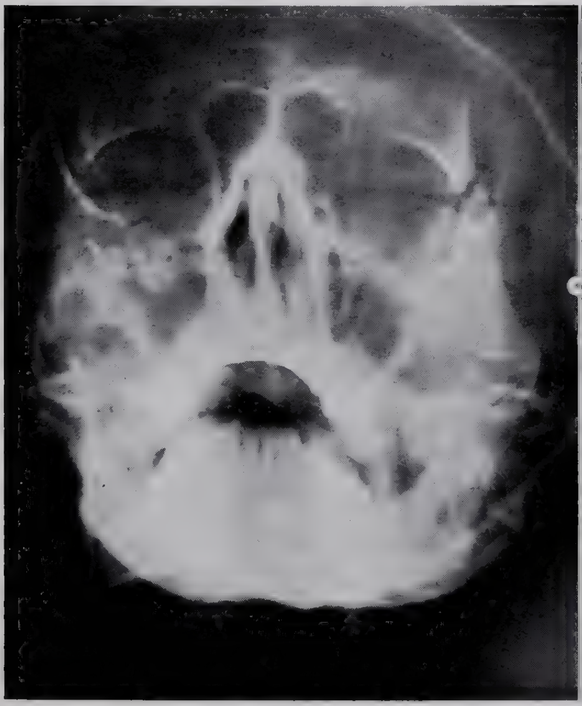

Figure 1-a

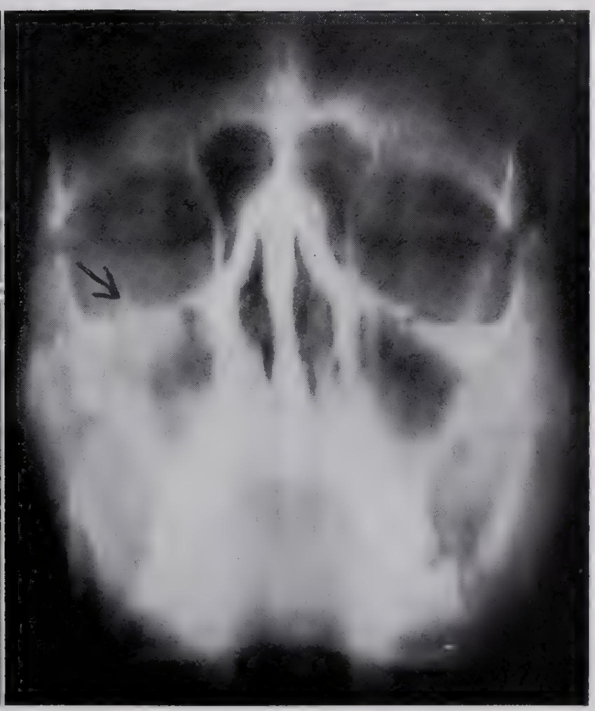

Figure 1-b

Continued

periorbital edema and ecchymosis, and subconjunctival hemorrhage. No other eye findings were noted on the initial examination. Roentgenograms demonstrated a right parietal skull fracture and bilateral frontozygomatic fractures.

The patient remained semicomatose for the ensuing three days, after which he became more alert and began to complain of double vision on upward gaze. Repeat examination revealed limitation of upward deviation of the right eye. Review of the x-rays was suggestive of an orbital floor fracture on the right (Figure 1a). Planigrams were obtained and demonstrated the fracture (Figure 1b).

The floor of the orbit was explored one week after the injury through an incision of the lower lid sulcus. An undisplaced fracture of the inferior orbital rim and comminution of the orbital floor were discovered. The inferior rectus muscle was freed from the floor fracture line and the floor elevated. The fragments locked into place, and the wound was closed. Postoperatively the patient was free from diplopia and made an uneventful recovery.

Discussion

This case demonstrates two of the four classic signs of orbital floor fracture: diplopia and x-ray evidence of fracture. These fractures are often seen on a routine Water's view and are usually well shown in AP planigrams. The diplopia is due to entrapment of or trauma to the inferior rectus or oblique muscles and is usually most obvious upon superior gaze. The dysfunction can be demonstrated with the traction test in which the eye is anesthetized with local Pontocaine, the rectus tendon is grasped with a forceps, and attempts at forced duction are carried out.

The third classic finding in floor fracture is enophthalmos due to loss of support of the globe. This, however, is often obscured by periorbital edema or depression of the orbital rim. The fourth finding is periorbital crepitance secondary to communication with the ethmoid or maxillary sinus. Other associated findings include a palpable step in the inferior rim, anesthesia or hypesthesia in the distribution of the inferior orbital nerve on the affected side, periorbital edema and ecchymosis, and subconjunctival hemorrhage.

If the possibility of an orbital floor fracture is kept in mind in the management of the patient with facial trauma, the diagnosis is usually readily made. Early surgical intervention can result in normal eye function and a good cosmetic result.

Laurence E. Winter, M.D.*
Melvin E. Sigel, M.D.**
Minneapolis, Minnesota

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**Clinical instructor, Department of Otolaryngology, University of Minnesota.

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Talk about lucky coincidences. The average adult has about 3,000 square inches of skin, which is just enough to cover him. — Changing Times

Neurological Conference

A Cerebrovascular Hemorrhage Due to Malformation*

Dr. Robert Soll

We have a case today of a young man, age 22, who had a cerebral hemorrhage resulting from a vascular malformation. In this condition about 70% of patients will present symptoms of either a spontaneous subarachnoid hemorrhage or a convulsion. Curiously, the most common cause of bleeding in teenagers and young adults is an arteriovenous malformation, whereas aneurysms are the most common cause in the older population.

History

While at work on June 22, 1965, this patient suddenly passed out during a coffee break. According to his wife he had had no previous history of seizures, nor had he complained of headaches or dizziness. Likewise, his general health had been good. Upon hospitalization in his home community, the patient was having major motor seizures. Examination at that time revealed fixed dilated pupils and bilaterally hyperactive reflexes and Babinski responses. On his third hospital day he developed pneumonia, which responded to chloromycetin and penicillin.

By July 8, 1965, the patient's condition had stabilized, although he was still semicomatose, responding only to deep pain. He was then transferred to the University Medical Center.

Physical Examination

Neurological examination at this hospital revealed an anisocoria,** the right pupil being larger than the left, and persisting hyperactive deep tendon reflexes of both upper and lower extremities with bilaterally positive Babinsky signs. His chest x-ray on the day following his arrival still showed a pneumonic infiltrate in the right lower lung. Films of the skull

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*Sponsored by the U. S. Public Health Service Grant N2502A63. These conferences are an integral part of the Comprehensive Clinic Program at the University of Minnesota Hospitals. The pediatric conferences are held every Wednesday from 1:00 to 3:00 p.m. The adult conferences are held every Thursday at 4 p.m. Co-ordinators for the project are Dr. Charles Branthaver and Dr. Edward Defoe, in Pediatrics, and Dr. Robert Soll, in Adult Neurology. Conference held September 9, 1965.

**See Test Your Word Score Page 943.

Continued

were normal. A lumbar puncture revealed an opening pressure of 134 mm.H_2O and a closing pressure of 94. The spinal fluid was xanthochromic and contained one neutrophile, four monocytes and 11 red blood cells of which about one third were crenated. The spinal fluid protein was 56 mg%, and the colloidal gold curve had both a first and midzone elevation.

Gradually the patient's consciousness began to clear. Beginning the third week of July, he could obey verbal commands to turn his head, lift his arm, etc. About that time he was started on oral feedings. By mid-August he was able to sit in a chair, read, and tolerate a normal diet, although he was still too weak to walk. An almost complete expressive aphasia, a right central facial nerve paresis, and a paretic right hand and arm remained evident during his early convalescent period.

Carotid Angiogram

A left carotid angiogram was performed, presumably because of his right hemiparesis; but no abnormality was found. A right carotid angiogram revealed a satisfactory filling of the intracranial vessels. There was a moderate-sized arteriovenous malformation located in the posteroinferior aspect of the right frontal lobe bordering on, or possibly extending into, the parietal lobe just above the sylvian vessels deep in the sylvian fissure. This malformation is fed primarily by one major branch of the middle cerebral artery which is definitely enlarged as compared with the other middle cerebral vessels in this area. The branch apparently comes to the surface from the sylvian fissure and extends upward a short distance before it dips back into the substance of the brain to feed the malformation. There is a slight depression of the sylvian vessels just below the malformation, and there appears to be about a 2 1/2 mm. shift of the internal cerebral vein towards the left. This would suggest a hematoma in the area of the malformation. The circulation through the malformation is moderately fast. Elsewhere the vessels are normal.

Dr. Bill Bradley*

The patient has an abnormal electroencephalogram. We can't tell that he specifically has an arteriovenous malformation but we can say that he does have a lesion which is causing destruction of part of his frontal lobe. There is no epileptiform activity.

Dr. Soll

The question might be raised: why was a right-sided hemiparesis and right central facial paresis more apparent clinically, when the lesion itself was in the right hemisphere? The most likely explanation is the so-called crus phenomenon in which a supratentorial tumor may produce uncal herniation resulting in compression of the contralateral peduncle against the sharp edge of the tentorium. Ipsilateral paralysis, paresis, or reflex changes may then be found.

Dr. Frank Meelhuysen**

I examined the patient yesterday to determine the extent of his present functional incapacitation. While walking he doesn't clear his feet well, although he is not shuffling. He tends to lose his balance, falling toward the right side which apparently is weaker. When asked to walk on his toes and heels, he did quite well. He also keeps his head slightly tilted to the right with his shoulder elevated on the left. The Romberg test is negative. In checking his strength I found that it was almost equal bilaterally, but reduced. This can be attributed partly to deconditioning resulting from prolonged bed rest. Range of motion is preserved in all major joints of all four extremities. I have noticed that people who lie in bed for a long time develop tight hamstrings, and this patient manifests this on straight leg raising. His ankles could be flexed just beyond 90°. Slight incoordination of the right leg is evident during heel to knee testing; however, this is not as marked as his hand incoordination during finger to nose testing. Proprioceptive* loss is not apparent in the upper extremities, although it is minimally demonstrable in the toes.

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*Assistant professor, department of neurology, University of Minnesota Hospitals.

**Assistant professor, physical medicine and rehabilitation, University of Minnesota Hospitals.

His wife mentioned that this man has difficulty in swallowing coarse foods such as meat. Liquids and soft foods can be handled quite well; but often he is afraid that he may choke. In view of this I checked his tongue motion and noticed that its movements are weak in all directions, and more so in tongue elevation. This can cause him difficulty in swallowing coarse foods because the tongue has to elevate to the roof of the mouth in order to move the bolus of food backward. There is a slurring of his speech, which can be accounted for by failure to make the right movements of his tongue. Dysdiadochokinesia of the tongue is present also, and there is a suggestion of tongue apraxia as well.

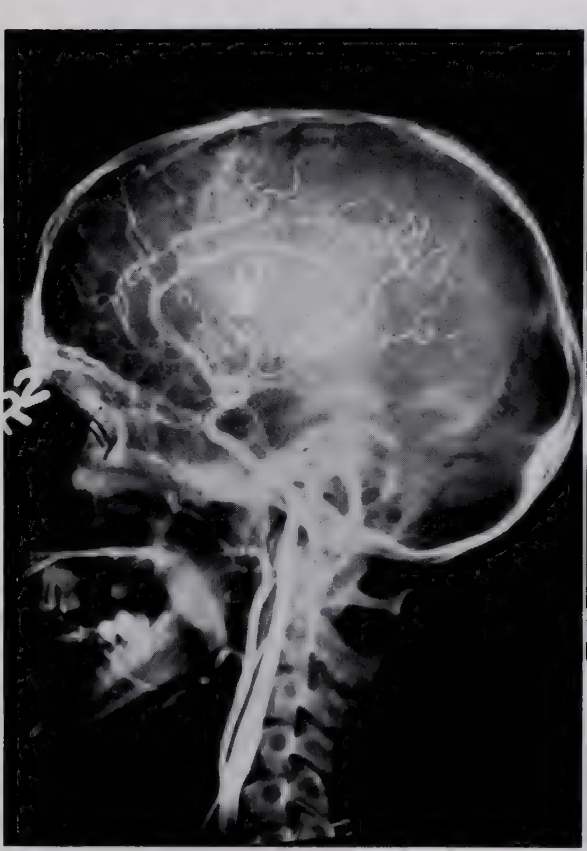

Fig. 1 — Angiographic demonstration of arteriovenous malformation situated just above the sylvian fissure in the posteroinferior lateral aspect of the right frontal lobe.

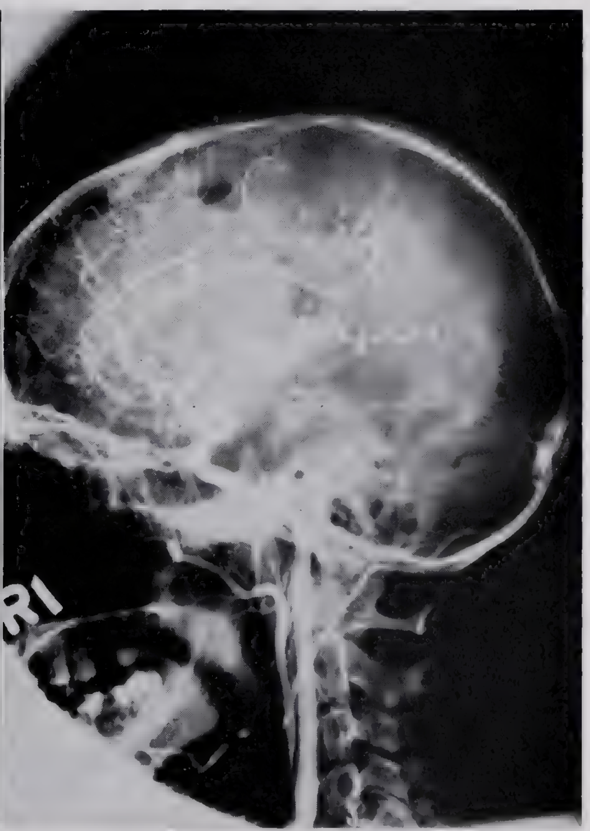

Fig. 2 — Right carotid angiogram showing surgical clips in region of the previously demonstrated A-V malformation.

Continued

Dr. David Danoff*

This lesion is in the right hemisphere which is probably the nondominant of the two hemispheres. A couple of facts that have to be considered are: first, there is a hematoma on the original angiogram which may account for his continuing weakness; and second, the vascular lesion is very likely still there. Occasionally a small malformation may bleed and subsequently destroy itself, causing no more trouble. The English have a large series of patients with subarachnoid hemorrhages upon whom nothing was found at the time of angiography and who have never bled again. They postulate, on the basis of autopsy reports on a few of these patients who finally did die, that they had had a small malformation which destroyed itself during the hemorrhage. This particular patient of ours, however, has what we call a giant malformation which would not be expected to destroy itself. We used to say that these things bleed repeatedly; that they are usually such small hemorrhages that a person may have a seizure or a headache and then get better; and finally, that until there was a definite loss of function, surgery was not necessary. In contrast, aneurysms produce a 50% mortality after the first hemorrhage; 50% of the remainder will bleed again in two weeks and 80% in a year. It is no longer felt that these lesions due to vascular malformation bleed repeatedly in a minor fashion, but rather that they are lethal or produce a moribund condition, as is the case with this patient. Since this lesion is in an area which is surgically accessible, it probably should be removed. In addition, the presence of a hematoma in this case would make the lesion more accessible, since it would establish a cleavage plane for the surgeon when enucleating the malformation.

Ligation of vessels may increase the degree of hemiparesis in this patient. When I saw him in clinic three weeks ago his hemiparesis was more profound than Dr. Meelhuysen has described it now, and I am surprised that he has improved this much. The presence of the hematoma may be causing part of his difficulty, and there is a distinct possibility that he may be stronger after its removal.

Mr. James Gilbertson**

The patient's verbal IQ is 80, his performance IQ is 65, and the full scale IQ is 72, placing him mentally in the moderately deficient range. Although he had average marks, he dropped out of school after the eleventh grade. I would estimate his premorbid intelligence to be around 95 to 100. The performance deficits suggest right-sided involvement. This is unfortunate for this patient because his strong areas before his illness were industrial arts and working with his hands. Now the presence of tremor and poor visual-motor integration make it almost totally impossible for him to do such performance tasks. Anything requiring speed or fast hand-eye coordination he is incapable of. Dr. Soll was interested in obtaining a baseline measure now, so that if an operation is done we can evaluate him afterwards to see if there has been any improvement. On the verbal tests I see no current evidence of aphasia. There is some loss of verbal skills, but performance and practical intelligence are most affected. He occasionally has some word-finding difficulties, but for the most part his communication is pretty good. His most noticeable speech problem is the dysarthria. The very low score on his Porteus test also suggests frontal lobe involvement. He is going to have trouble with vigilance, remaining alert, and making common sense decisions.

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*Medical fellow neurosurgery, University of Minnesota Hospitals.

**Clinical psychology trainee, University of Minnesota Hospitals.

Dr. Meelhuysen

His wife mentioned that when he eats, he always finishes the left side of his plate first and has to be reminded several times to finish eating from the whole plate; so there might be a suggestion of visual field loss on the right side. I just wondered if you noticed this in his reading.

Mr. Gilbertson

I had him do some tasks; for example, there is one sub-test in the WAIS in which you have to pick out the missing parts, and he did fairly well on that. He also had to put together small pictures in order, nonverbal synthesis is what we call it, and he did fairly well on that too.

Mrs. Judy Edmands*

His oral reading was slurred, but he was getting all the words and there was no difficulty in rate or rhythm. Comprehension of silent reading was performed well with sentences but poorly with paragraphs.

Dr. James Story**

With all these findings I would still be concerned about a lesion in the left hemisphere. He may also have a field defect on the right. In addition, he is dysphasic and has a right hemiparesis.

Dr. Meelhuysen: He was originally classified as having total aphasia, but this is now reduced.

Dr. Soll

There was a very tiny anterior cerebral artery from the internal carotid to the mid-line which filled both anterior cerebrals as compression was applied to the right carotid artery. The remaining vessels appeared normal, however, and no contrast media passed over to the right middle cerebral.

Dr. Story

It is not uncommon to have an aneurysm associated with a malformation; also, the reason that the left anterior cerebral does not completely fill could be due to spasm related to an aneurysm. There is a configuration of the vessels on the right suggesting a hematoma but there is no appreciable shift. If you expect to explain everything on the basis of a crus phenomenon, I would expect more of a shift towards the opposite side; therefore I am somewhat disturbed by what I see.

Many of his signs and symptoms were suggestive of an aneurysm of the middle cerebral artery: the aphasia, the transient right hemiparesis, the visual field defect, and a little elevation of the left middle cerebral

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*Department of audiology, University of Minnesota Hospitals.

*Assistant professor of neurosurgery, University of Minnesota Hospitals.

Continued

artery. The original conclusion on angiography was probably correct, but I am not entirely satisfied. In view of his clinical history I would do another left carotid angiogram before I tackled the malformation.

Dr. Meelhuysen: What is the incidence of vasospasm just after the onset of the subarachnoid bleeding? Could this account for the transient symptomatology that we see here on the opposite side?

Dr. Story

Vasospasm is very common. I think it is almost invariable. It could, account for the symptoms, but usually the vasospasm is most marked on the side of the aneurysm. In treating malformations surgically we have a number of criteria we go by: the presence of intractable seizures or intractable headaches would favor surgical intervention; a persistent or progressing neurological deficit might be construed as an indication for surgery; repeated hemorrhage is an obvious indication. As far as this particular lesion is concerned, I would recommend resecting it, since it looks as if it arises from the peripheral portion of the middle cerebral artery. It is a relatively small lesion, and as a result of the hemorrhage and hematoma a capsule around the lesion has probably formed. This encapsulation would make the removal a bit easier.

Student: How soon do you like to do surgery?

Dr. Story

As soon as the patient's condition permits, if the criteria or indications for doing it are present. This patient has a persistent neurological deficit and is probably going to bleed again.

Dr. Meelhuysen

Does the bleeding occur as a result of pressure; or what is the basic cause of bleeding in such a malformation?

Dr. Story: There is increased pressure within the veins, enhancing their tendency to bleed. Possibly straining will contribute to it, though hemorrhage can occur at any time.

Dr. Soll: What are the chances of doing this operation without producing a further neurological deficit?

Dr. Story: They are pretty good, especially in view of the severe hemorrhage he had with hematoma formation.

Miss Helen Kretchmer*

I talked to the patient, his mother, and his wife, and they are in complete accord with what has been suggested for his treatment. Both he and his wife come from large families. The educational level in his family is about to the sophomore or junior year in high school, indicating that they are probably in the lower range of average mentality. The father works in a feed plant in their home town. The mother is a cook in an all-night restaurant. The wife has been a waitress in the past and has done some babysitting up to the time the patient came home. They knew each other two and one-half years before they were married. There will be problems in the future for this young couple because of his great disability, but they do not complain. The family has been helping to support them. At the time he was in the hospital there was some question of initiating assistance from the welfare board.

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*Supervisor and assistant professor social service, University of Minnesota Hospitals.

Dr. Story

Another consideration is the psychological problem, which can be difficult. If he has been advised that the malformation might bleed again, this can be a real handicap. We recently operated on an individual at the Veterans Administration Hospital who was an invalid from this standpoint. He has improved tremendously with the successful removal of his vascular malformation.

Dr. Soll

Many of these malformations are situated in the frontal lobe and for this reason may be prone to cause psychological disturbances. This is another common feature of vascular malformations. Dr. Story, would you do anything about surgery until after the termination of his wife's pregnancy, or would this have any bearing on planning his treatment?

Dr. Story: I don't think there is any great hurry. I don't know when the lesion will bleed; it could bleed today, I suppose, but my feeling is that I wouldn't be in any great rush about it.

Dr. Meelhuysen: When would you plan to repeat the angiogram?

Dr. Story: Just prior to operating on him.

The Patient Is Presented and Examined

Dr. Danoff: When we saw the patient in consultation in clinic he was unable to walk without assistance.

Dr. Story

He is still obviously and strikingly impaired mentation-wise, which makes me a little bit less eager to operate on him at this time. We probably would be able to remove the lesion without injuring him and thereby prevent him from having subsequent hemorrhage, but this is probably not going to help him in his over-all intellectual functioning.

Dr. Soll: It may be worthwhile to wait a few months and then repeat the psychological tests. My first inclination was to wait and possibly not even do surgery. You try to think about what you would do in your own case: whether you would want to live the rest of your life as a hemiparetic (a possible eventuality of surgery) or take the chance of bleeding again in order to be certain of retaining what function you have.

Dr. Story

I don't think the possibility of a paresis here is the big factor that is dissuading me. What makes me hesitant is his present intellectual incapacitation. Is he going to be a contributing individual; is he going to be

Continued

able to support his family; or is he going to be a burden to his family or the state?

Mr. Gilbertson

The most significant impairment for him right now is in practical functioning intelligence. Verbally he scores an IQ of 80, which isn't too bad, but it is lower than he was premorbidly. He has a 65 IQ on performance tests, which of course means that the only employment for him would be a simple task-oriented job. I would recommend waiting three months in order to obtain a significant re-evaluation psychologically. He has made rapid improvement to date, although I don't think he will keep improving at this rate.

Dr. Story: I think if he improved a great deal in the next two months, one would be inclined to be more vigorous with respect to surgical treatment.

Dr. Soll: If he doesn't improve, would you still be reluctant to operate; or under what circumstances of clinical change would you consider an operation?

Dr. Story

If he does not improve, I would not operate on him. If he should bleed again or develop uncontrollable seizures or progressive deficit, I would operate.

Mr. Gilbertson

He might do well in a really structured situation where he didn't have to do fine, coordinating-type work. He said he made furniture,—I don't know what that involves, but he doesn't seem to be impaired in gross motor activity of the very simple type. I don't know whether this disability will clear up or not, or whether he can be trained; but any job that demands speed, foresight or planning is beyond him at this time.

Dr. Meelhuysen

Recuperating from a vascular accident is slow, but the environment can be conducive to a patient's improvement. So when the mother, for instance, was so eager to help him with buttoning his shirt, I urged her to let him do it himself. Presently it takes him more time, but he is better off by helping himself. Another problem is his poor bladder control, particularly at night. Here again we have to teach the patient to go to the bathroom at more frequent intervals and to minimize fluid intake before retiring. Simple exercises can be demonstrated and taught to patients with incoordination. Some Frenkel's exercises for the legs, such as the heel to knee maneuver, are beneficial. For the upper extremities, a peg-board type of approach can be used in which one takes small objects out of a hole and replaces them. Finally, he should gradually participate in doing simple household activities. At present he does nothing; in fact, he is in bed most of the time.

Dr. Soll

In summary, we can recommend that he increase his activities in order to try to increase his functional ability at home. After two or three months we can repeat the psychological, neurological and physical medicine evaluation, following which another neurosurgical opinion can be obtained regarding surgery.

Robert Soll, M.D.
University of Minnesota

Addendum

The patient was readmitted to the hospital approximately two months following the conference. A left carotid angiogram was repeated and showed no evidence of a lesion in the left hemisphere. Subsequently an intra-arterial injection of Amytal confirmed the presence of speech dominance in the left cerebral hemisphere. The patient then underwent a successful craniotomy and removal of the A-V malformation. Two months following surgery he began part-time employment.

Participating in the conference were Miss Helen Kretchmer, Supervisor and Assistant Professor Social Service; Mrs. Judy Edmands, Department of Audiology; Dr. James Story, Assistant Professor of Neurosurgery; Mr. James Gilbertson, Clinical Psychology Trainee; Dr. Frank Meelhuysen, Instructor, Physical Medicine and Rehabilitation; Dr. Bill Bradley, Assistant Professor Neurology; Dr. David Danoff, Medical Fellow Neurosurgery and Dr. Robert W. Soll, Neurologist.

The Tobacco Tyrant*

Armstrong finds that cigaret smoking contains 1 per cent of carbon monoxide, while quickly-smoked Havana cigar contains 5 per cent.

Dixon demonstrated that the blood in cigaret smokers may contain 5 per cent of carbon monoxide. He believes that the effects of cigaret smoking are chiefly due to carbon monoxide.

Gies, Kahn & Limerick say tobacco smoke also contains collidin, aldehydes and carbon monoxide.

Huchard speaks of nicotin as a cause of arteriosclerosis. He proved this experimentally by injection of nicotin into rabbits.

Furbringer regards nicotin as the most toxic substance in tobacco smoke. It varies in quantity, according to him, from 2 to 7 per cent. The fresher the tobacco, the richer is the distillation product of nicotin. He asserts that the smoke from a pipe is freer from nicotin than that of a cigaret, and that inhalation of smoke into the bronchi increases the absorption of nicotin eight times.

Cushney showed that experimental nicotin injection "disturbed cardiac rhythm mainly by a neurotropic influence upon the ganglionic terminations of the vagus and sympathetic nerves." There may, therefore, be two opposite effects, slowing or acceleration, depending on the preponderance and selective action on the two nerves.

To be continued.

E. O. Giere, M.D.**
Minneapolis, Minnesota

**Editor's Note: In 1928 Dr. E. O. Giere prepared and presented a manuscript at one of the Twin City hospitals on the evil effects of tobacco.*

***Through the courtesy of his sons, Doctors Richard and Joe Giere, the timeworn and faded manuscript was made available to the editor. Excerpts will be printed serially.*

See Minnesota Med 48:1687, 1965.

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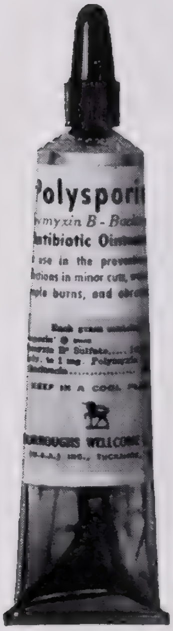

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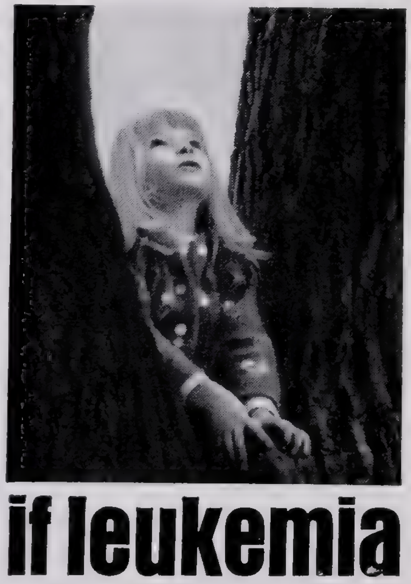

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THIS SPACE CONTRIBUTED BY THE PUBLISHER

Medical Seminar

Hearing Loss and Delayed Speech Development

Techniques for Evaluating Auditory Acuity of Infants and Young Children

Presented as a Seminar

Sponsored by

The Faculty of the Mayo Graduate School of Medicine

KNOWLEDGE OF the techniques for evaluating auditory acuity in infants and young children is mandatory for those confronted with the task of diagnosing auditory disorders in this age group. Prompt detection and proper evaluation of such disorders are important, since delay augments frustration, propagates retardation, and hinders the vital education and rehabilitation of those afflicted.

The purpose of this paper is to outline the problems in the differential diagnosis of infants and young children with delayed speech development, impaired hearing, or both and to present the methods used in evaluating auditory acuity in these patients.

Differential Diagnosis

Perhaps the most frequent presenting symptom in a child with a communicative disorder is the parents' complaint that the development of speech has been delayed. The pronouncement that a child fails to speak solely because he cannot hear may indicate an erroneous or incomplete diagnosis, for the differential diagnosis of delayed speech development, failure to respond to auditory stimuli, or both, includes not only peripheral hearing loss but also aphasia, emotional disturbance, and mental retardation.

A rational approach to diagnosis, propounded by Myklebust,[1] includes taking a detailed history, assessing behavior, and considering the results of auditory testing. A complete history includes a search for those factors (Table) which might contribute to the etiology.

Frequently the history obtained during the pediatrician's and neurologist's examinations may quickly lead the examiner to the

Some Etiologic Factors Related to Hearing Loss and Delayed Speech Development

Hereditary	Prenatal	Natal	Immediately Postnatal	Infancy and Childhood
Familial deafness	Rubella in first trimester	Prematurity	Asphyxia neonatorum	Meningitis
	Rh incompatability	Lengthy labor	Jaundice	Measles
	Trauma	Type of delivery	Convulsions	Influenza
	Emotional disturbance	Difficulty of delivery	Apathy	Pneumonia
	Medication			Encephalitis

Continued

proper diagnosis. Since this is not always the case, the analysis of behavior becomes an integral part of the total evaluation of the child. Although behavior is a subject in itself, the salient features which characterize the child with a hearing loss, the mentally retarded child, the aphasic child, and the child with psychic deafness will be mentioned for the purpose of differential diagnosis.

Peripheral Loss of Hearing

If residual hearing is present, children with peripheral loss of hearing usually respond to loud sounds much more consistently than do those having the other disorders mentioned. Characteristically alert, these children compensate readily for their auditory handicap by using other sensory modalities. For example, they display a marked sensitivity to tactile and visual stimuli — in contrast to those who have aphasia, mental deficiency, or psychic deafness. Also, children having severe peripheral hearing impairment typically have a monotonous, nonmelodious vocal quality. The aforementioned characteristics may be muted by superimposed emotional disturbance or mental retardation.

Aphasia

This term implies that underlying brain damage is the cause of the speech disorder. Some authors contend that central damage alone does not produce a reduction of hearing acuity.[2] With auditory sensitivity intact, aphasic children may not vocalize because they are unable either to comprehend speech (sensory or receptive aphasia) or to store speech and to use language (motor or expressive aphasia). Youngsters with sensory aphasia, which is considered to be the more common form, are more likely to be misdiagnosed as having peripheral loss of hearing; patients having motor aphasia generally respond normally to auditory stimuli.

The aphasic child usually has some degree of incoordination and generally lags in motor development when compared with other children of his chronologic age. The compensatory function of other sensory modalities is perceptibly absent. Hyperactivity and distractibility dominate the behavior of aphasic children, while meaningless jargon of good tonal quality distinguishes their particular attempts to verbalize. These children actually use different sounds when referring to the same object. Despite the rampant bursts of jargon, the aphasic rarely gestures or vocalizes during play situations.

Psychic Deafness

A clue to this diagnosis may be revealed through a history of gradual withdrawal by the child after he has developed some verbal language. This may persist until he relinquishes both speech and auditory contact with the surrounding environment. There is, of course, as wide a spectrum of psychic pathology as there is of the severity of hearing impairment associated with peripheral hearing loss.

Autistic children may be completely mute in contrast to both aphasic children and those having peripheral loss of hearing; however, when they vocalize, autistic children usually have normal tonal quality. A high-intensity, low-frequency sound with its resultant pronounced tactile sensation often fails to evoke a response as it might in the peripherally deaf child. Some of these children with psychic deafness exhibit profound fear of sound. On the other hand, incongruous, subtle, indirect responses to faint sounds may be observed.

Behavior is often quite bizarre and distinctly devoid of emotion. Motor ability is usually rather good in contrast to that of aphasic and mentally retarded individuals.

Mental Deficiency

Mentally defective children cannot perform as well as normal children of the same chronologic age. One would then anticipate a history of delayed motor and emotional development. These children generally vocalize with a normal voice quality and employ gestures within the limits of their ability. Usually they respond to familiar environmental sounds, but failure to react to pure tones or conversation certainly does not make the diagnosis of peripheral deafness and exclude that of mental deficiency. Unlike that of children with psychic deafness, the behavior of mentally deficient children is not bizarre.

Techniques for Evaluating Auditory Acuity

Tests Applicable to Infants and Children to Three Years of Age

The conventional modes of evaluating adult auditory acuity are often unsuitable for infants, because infants frequently lack the cooperation and responsiveness required to adequately assess auditory capacity by these means. Therefore, one must employ pragmatic techniques, especially for infants having a high risk of deafness, such as those with a history of Rh incompatibility, maternal rubella in the first trimester of pregnancy, cerebral hypoxia (during labor or resulting from birth trauma), and familial hearing loss.

Some of these tests are gross at best, and the evidence obtained usually depends on observations of the infant's behavior when a test sound is produced. Perhaps one of the best-known gross-behavior responses is the palpebral reflex which has been well documented and employed by many.[3] These tests are not intended to measure the threshold of hearing but are used as screening devices.

The distraction technique depends on the Moro or startle response, such as crying, turning of the head and torso, and cessation of activity in response to a sound. Here various acoustic stimuli, such as the sound of wooden clackers, bells, rattles, and so forth are presented out of the baby's peripheral vision, and the startle response is observed and recorded. Reproducible test situations can be created when the noisemakers have been calibrated as to frequency and intensity and their sounds have been stored on tape.

Suzuki and co-workers[4] tested newborn infants with pure tones of high intensity and concluded that "the most serviceable aural responses in the newborn infant are (1) blinking, (2) jerking of the body, and (3) sudden deep inspiration, and that the use of these three responses in combination with each other as criteria of neonatal hearing may constitute the most effective and reliable method for clinical audiometry of newborn infants."

Again, the concept behind this type of gross testing of high-risk infants is to determine which of them need more accurate evaluation of auditory acuity at a later date. The parents should be advised that these early reports are only tentative impressions, for many examiners have dealt with the complex problems arising from premature "definitive" diagnosis.

Other techniques have been devised in an attempt to evaluate accurately the auditory acuity of infants and young children. These tests are essentially electrophysiologic procedures designed to measure the threshold of hearing in difficult cases. Three types of electrophysiologic procedures have been mentioned in the literature — namely, electrodermal audiometry, electroencephalographic audiometry, and cortical audiometry.

Electrodermal audiometry (EDA) (psychogalvanic skin resistance audiometry is the older term) was first clinically introduced by Bordley, Hardy, and Richter[5] in 1948. This technique is essentially based on the sympathetic nervous system response to a mild electric shock. Skin resistance as measured by a galvanometer is the unconditioned response to the unconditioned electric shock, while the pure tone is the conditioned stimulus. After several shock-pure tone presentations, changes in electric skin resistance compared to a known resistance occur as a response to the pure tones alone without a concomitant shock; hence, conditioning has occurred and an attempt is made to determine auditory thresholds.

The clinical applicability of this method may be seriously affected by extraneous physical movements, certain endocrine problems, electric interference, and various nonauditory stimuli. After being shocked, many patients become anxious, uncooperative, and quite negative. Despite these serious limitations, electrodermal audiometry may still have a role in the total evaluation of the infant and young child with a hearing disorder.

The second electrophysiologic method is

Continued

based on electroencephalographic changes to auditory stimuli. Marcus, Gibbs and Gibbs,[6] in 1949, first reported on the use of electroencephalography as a means of diagnosing hearing loss in very young children. Electroencephalographic audiometry is still essentially in the research and development stage. This test can be performed only on sleeping patients, but it does not require preconditioning. Electroencephalographic audiometry has been employed in the case of infants under 18 months of age, below which electrodermal audiology is normally limited by the infant's high skin resistance.

The decisive drawbacks to electroencephalographic audiometry are the difficulty in interpreting the response patterns to auditory stimuli and the fact that an accurate threshold cannot be determined.

The third and most recent electrophysiologic method for evaluating auditory acuity is termed cortical audiometry. Cody and Bickford,[7] in 1965, introduced cortical audiometry as an objective test for evaluating auditory acuity in man. Here sophisticated computer-averaging techniques are employed to record averaged, evoked, cortical responses to auditory stimuli. By this technique, the auditory acuity in the speech frequency range (500, 1,000, and 2,000 cps) can be accurately determined for each ear in the awake, naturally sleeping, or sedated infant.[8]

Cortical audiometry promises both a simplified answer to the interpretative problem which still vexes the proponents of electroencephalographic audiometry and an objective means of accurately evaluating auditory threshold levels in infants.

Tests Applicable to Preschool Children

For testing preschool children, a great deal of credit goes to Ewing and Ewing[9] of England, who have worked for years testing and evaluating infants and children with hearing problems. They shunned pure-tone audiometry for this age group and based their methods on common sounds of the home environment, such as the tinkle of a teaspoon against a cup. Some workers object to the use of noisemakers; for the information is nonspecific, and the child can be better evaluated through history, interview, and physical examination.

Perhaps the single most useful established method of evaluating preschool children is play audiometry.[10] This consists of a short period of conditioning with the child listening to tones at relatively intense levels. When the tone is presented, a specific play action must be accomplished by the child, such as putting a ball in a box. Interest is maintained by changing the objects and games which serve as a reward for having heard the sound. When earphones are rejected, the tones are presented from a loudspeaker.

Most children can be play-conditioned, and the few who are unconditionable usually have problems other than, or in addition to, their peripheral hearing impairment.

Numerous variations and innovations of play audiometry have appeared in the literature. Some innovations were constructed to capture and maintain the interest of the child being tested. The peep show of Dix and Hallpike[11] of England, applicable for three-year-olds, was the first of many modifications of conventional play audiometry.

Ordinarily all of these tests are useful for children from three to six years of age, and complete audiograms usually can be obtained. Most children tolerate the earphones and respond satisfactorily to the standard pure tones. The peep show and its variations are not necessary as a routine procedure, for good results usually are obtained through conventional play audiometry.

The play situation has also been used for the development of discrimination tests for children. Keaster's[12] technique is suitable for determining the speech threshold for children from three to six years of age.

The electrophysiologic tests also can be used quite effectively for children in the preschool age group. The efficacy of these techniques, especially of cortical audiometry, can be demonstrated when dealing with uncooperative children who present difficult problems of diagnosis and who cannot be adequately evaluated by conventional play audiometry.

Comment

Infants and children having delayed speech development, hearing disorders, or both can present a formidable problem of differential diagnosis. Early diagnosis is essential to avert an irreversible speech handicap and to ensure optimal results through rehabilitative measures. It is important to recognize that pathologic conditions other than peripheral hearing loss may be responsible for delayed development of speech. A rational team approach, including the talents of the pediatrician, neurologist, psychiatrist, audiologist, psychologist, and otolaryngologist, may be required to separate the aphasic, the autistic, or the mentally retarded child from the child having peripheral hearing loss.

The correct diagnosis can usually be made from history, physical examination, and assessment of behavioral symptomatology and the results of auditory testing. On occasion it may be necessary to reevaluate patients with difficult diagnostic problems at a later date. This is especially true when varying degrees of mental retardation and emotional disturbance are superimposed on a child with peripheral hearing loss. The exact nature and reason for delayed speech development may not be discovered in some instances even after the most thorough investigation.

Gross testing can effectively determine which infants need more accurate evaluation of auditory acuity in the future. Cortical audiometry promises to be an objective means of evaluating auditory threshold levels in infants. It can also be used to advantage for preschool children and in those cases where conventional play audiometry is either unrevealing or impractical.

Summary

The most frequent indication of loss of hearing in a child is delayed development of speech. The differential diagnosis chiefly involves (1) peripheral loss of hearing, in which the child characteristically is alert and compensates for his handicap by using other sensory modalities; (2) aphasia, in which the child usually has some degree of incoordination and lacks the ability to compensate with other sensory modalities; (3) psychic deafness, in which the child usually has developed some verbal language and then has abandoned it in a general withdrawal from the environment; and (4) mental deficiency, in which general development is retarded but tonal responses tend to be normal.

Gross testing of auditory function in infants provides information of screening value only. Startle responses to auditory stimuli are most often used in these tests. Electrophysiologic techniques have been devised in attempts to acquire more definitive information. Electrodermal audiometry is based on a conditioning procedure and is affected by many extraneous factors. Electroencephalographic audiometry presents problems of interpretation and can be used only on sleeping patients. Cortical audiometry employs computer-averaging techniques and can accurately determine auditory acuity in infants and young children.

Perhaps play audiometry is the best established method for evaluating preschool children. However, the electrophysiologic techniques may be useful, particularly in the examination of uncooperative children or those with difficult problems of diagnosis.

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Rochester, Minnesota

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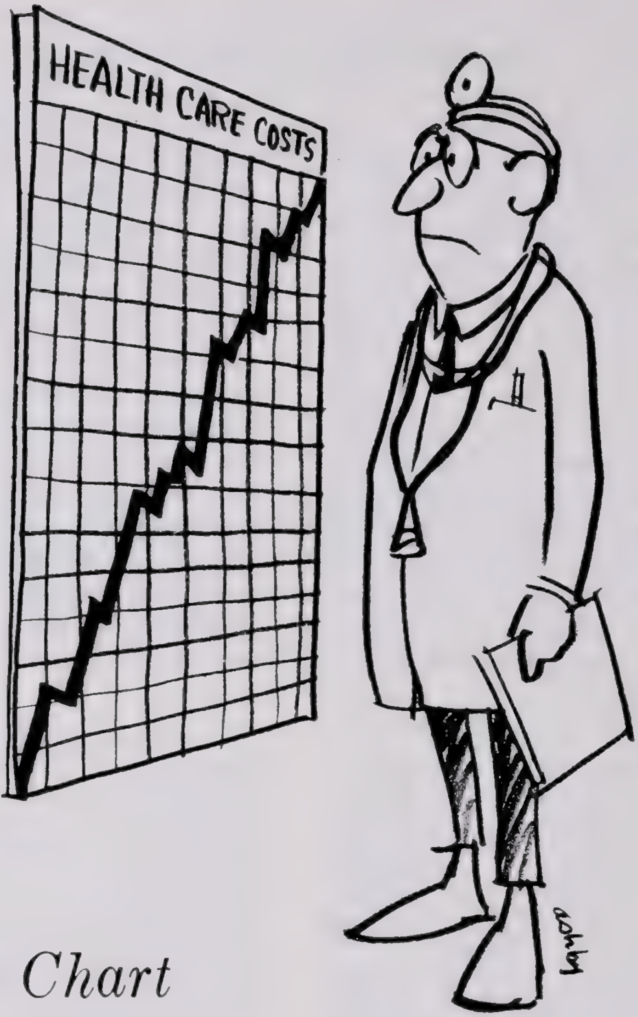
3. Froeschels, Emil, and Beebe, Helen: Testing the Hearing of Newborn Infants. Arch Otolaryng 44:710, 1946.

4-12 May be secured from the author or the reprints.

How can I tell what I think till I see what I say. — Forster



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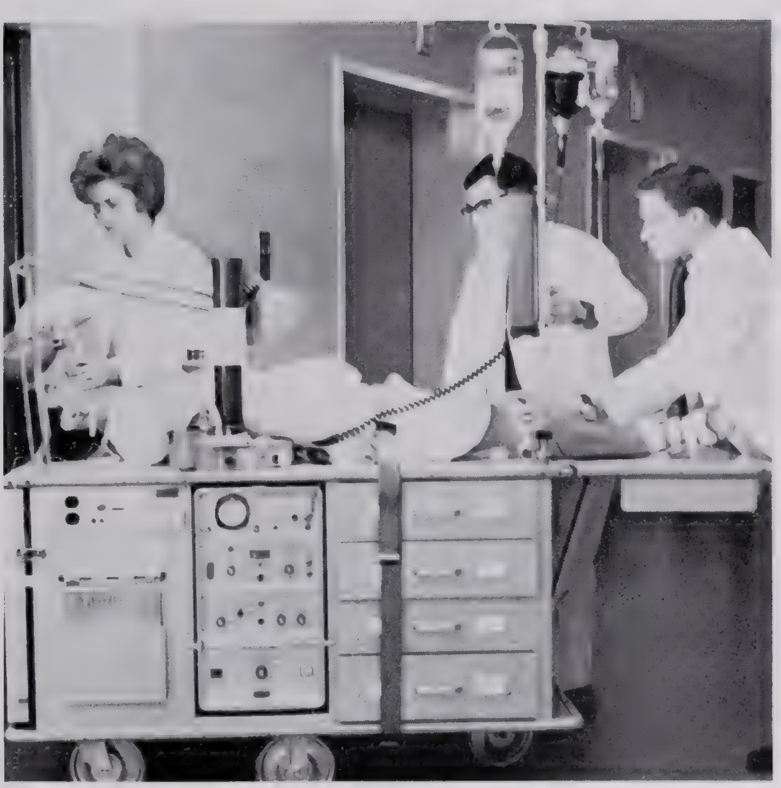

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Clinical Path Conference

Heart Failure and Abdominal Pain

Case Report

A 55-year-old married white female was admitted to St. Barnabas Hospital on April 6, 1960, for evaluation for mitral commissurotomy. She had had known mitral stenosis for ten years and for five years had been treated with quinidine and digitoxin for auricular fibrillation and congestive heart failure. In early 1959 she had an episode of lower leg pain, and a saddle embolus was removed from the abdominal aorta at the iliac bifurcation. She was placed on long-term dicumarol and improved. In the next year she developed increasing shortness of breath, paroxysmal nocturnal dyspnea, and a fifteen to twenty-pound weight loss. She had experienced periodic epigastric pain for three months before admission. The pain occurred after meals, awakened her at night, and was occasionally associated with diarrhea. The pain always subsided spontaneously.

Physical Examination

The patient was a middle-aged dyspneic female. Her blood pressure was 120/76 and her pulse was 80 with an irregularly irregular rhythm. The heart was enlarged. A diastolic rumble, a loud apical first sound, and a diastolic blow over the sternum were heard. The right side of the chest did not expand, and diminished breath sounds were heard over the right lung. The right chest was dull to percussion. Abdominal examination disclosed no masses or tenderness. A well-healed appendectomy scar was present. Both lower extremities showed pitting edema. The admitting diagnosis was mitral stenosis with right pleural effusion.

Laboratory Data

Laboratory work on admission included a prothrombin time of 22.5 seconds, a hemoglobin of 14.9 gm.%, and a WBC of 15,000 with 85 PMNs, a sedimentation rate of 46 mm./hr., a normal urinalysis and normal electrolyte studies. The electrocardiogram was abnormal with a right bundle branch block and digitalis effect.

Course

On the first hospital day, 1400 cc. of clear fluid was removed from the right chest. It had a protein content of 3.3 gm.%, a specific gravity of 1.016, and contained no organisms on gram stain. A culture of the fluid showed no growth. Her respiratory symptoms improved, but she began to complain of mild epigastric pain and two to three watery stools a day. On April 10 she vomited and complained of severe abdominal pain localized to the epigastrium. The pain became generalized. The blood pressure was 200/70 and the pulse 30 to 50. Examination showed abdominal distention without bowel sounds. Repeat laboratory studies included a prothrombin time of 17.5 seconds, a transaminase of 25 units, a WBC of 21,000, and a hemoglobin of 18.0 gm.%. No amylase was done. A laparotomy was performed, but the patient did not improve. Her temperature rose to 105°. Her electrolytes included a sodium of 147 mEq/L, a chloride of 88 mEq/L, a carbon dioxide of 32 mEq/L, and a potassium of 5.3 mEq/L.

Continued

Her BUN was 42 mg.%, and her prothrombin time was 52 seconds. No bilirubin was done, but her skin was icteric. After three days in the hypotensive state maintained by levophed, she died on April 14.

Dr. Lyle Hay*

Dr. Mork, may we see the x-rays of the chest and abdomen?

Dr. Frank Mork, Jr.**

A P.A. film of the chest on April 6 shows cardiac enlargement with straightening of the left heart border (Figure 1). This is characteristic of mitral valvular disease. The pulmonary and vascular markings are prominent, but the lungs are not edematous. There is an increased density at the right base extending up along the right lateral chest wall, which indicates probable pleural fluid. A repeat P.A. chest film the following day shows reduction in the right pleural fluid with residual underlying parenchymal changes that could represent atelectasis. A focus of pneumonia or a pulmonary infarct cannot be excluded. Flat and upright films of the abdomen, taken on April 10, show distention of the small bowel in the mid and lower portions of the abdominal cavity (Figure 2). On the supine film there is a suspicious small air bubble which could be within an abscess cavity but more likely is air within the duodenal cap. I see no evidence of free intraperitoneal air or fluid within the abdomen. There are no masses. The films incidentally show calcifications which are probably renal calculi overlying both kidneys. One would have to obtain an intravenous pyelogram for better evaluation.

Discussion

Dr. Hay

First, I assume this patient has had rheumatic heart disease with subse-

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**Radiologist, St. Barnabas Hospital.

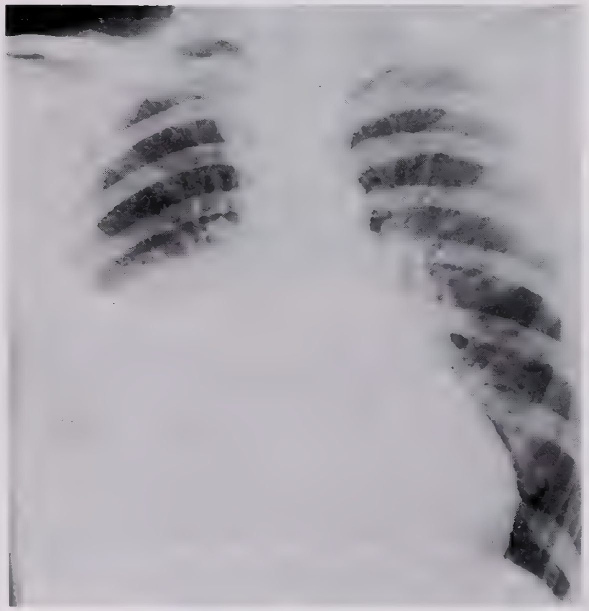

Fig. 1 — Film of chest taken on day of admission showing right pleural effusion and cardiac silhouette of mitral stenosis.

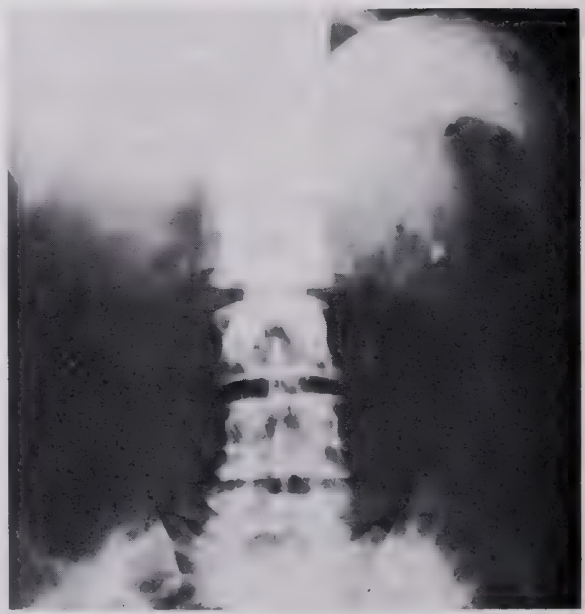

Fig. 2 — Abdominal film showing dilated small bowel loops. No masses or fluid are seen.

quent mitral and possibly aortic valvular lesions. She has dyspnea with auricular fibrillation and a history of an embolus. She is decompensated with secondary pleural effusion, which could be due to an abdominal condition. Patients with pancreatitis get pleural fluid, usually on the left side and related to abdominal effusion. Although pleural fluid can be seen on the films, abdominal fluid is absent. There is no increase in the liver to suggest a subphrenic process with pleural effusion. Whether or not she has had a pulmonary infarct is difficult to tell. It is more likely she has atelectasis from pleural effusion. The effusion fluid was a transudate because of the relatively low protein content and the specific gravity of 1.016.

Chronic Mesenteric Insufficiency

She has had epigastric pain which increased after meals and was accompanied by weight loss. This triad of symptoms has been ascribed to chronic mesenteric arterial insufficiency. I wonder if she has had an embolus to the mesenteric vessels with a partial occlusion. To be symptomatic, two of the three vessels that form the collateral blood supply to the intestine have to be closed. These vessels are the celiac axis, the superior mesenteric, and the inferior mesenteric. If only one vessel is gradually closed, collateral circulation will develop. Several times I have seen a large mesomesenteric artery coming up from the inferior mesenteric and entering the superior mesenteric just beyond its origin when there has been a block of the point of origin of the superior mesenteric from the aorta.

Pancreatitis

Pancreatitis should have been suspected when she complained of epigastric pain on April 19. She had nausea, vomiting, dull abdominal pain and dehydration. Hemoconcentration is common in pancreatitis. Her hemoglobin rose from 14.9 grams to 18 grams. This is certainly a reflection of hemoconcentration. She may have had an effusion into the peritoneal cavity, which we don't see, or she may have lost plasma into an organ such as the small bowel damaged from ischemia. If she had an edematous pancreatitis she could have had a retroperitoneal plasma loss. If she had a hemorrhagic pancreatitis, her transaminase would be elevated well above 25 units. Unfortunately, she did not have serum or urine amylase. This is unfortunate, because any patient who has an acute abdominal illness or catastrophe should have an amylase. In general, patients with pancreatitis should not be operated upon.

Mesenteric Thrombosis

In this patient with a history of mitral stenosis, with cardiac decompensation and previous history of an embolus to the aorta, the most likely abdominal catastrophe is an occlusion from an embolus. On the abdominal x-ray the small bowel is primarily affected. If the entire superior mesenteric artery is blocked, the ileocolic branch is usually blocked as well; and the right colon to the midtransverse colon is involved. I see no distention of the cecum or the hepatic flexure or transverse colon. The x-ray is not consistent with an ileocolic branch block, but this may be because the embolus has gone beyond the ileocolic vessel.

We weren't told whether this patient had fecal vomiting. She did have a

Continued

previous appendectomy; so a mechanical small bowel obstruction secondary to adhesions following the appendectomy cannot be excluded. We are told she had a silent abdomen. A silent abdomen is not characteristic of mechanical obstruction; so this must be a paralytic ileus.

I conclude that the most likely diagnosis in this patient would be a mesenteric embolus lodged beyond the ileocolic branch of the superior mesenteric artery, which accounted for her hypotension after the laparotomy and led to hemoconcentration. The rise in the white blood count from 15,000 to 21,000 is probably secondary to hemoconcentration. Other evidence for hemoconcentration is the elevated BUN and the electrolyte changes. Terminally she was in a hypotensive state maintained by levophed. I hope the clinician gave her levophed because he considered her to be in irreversible shock. In general, plasma or lactated Ringer's solution is better than vasopressers for patients with hypovolemia and hemoconcentration.

Jaundice

The presence of jaundice is a further indication of profound heart failure with increasing liver congestion. If you add hypotension and vasopressors as further insults to the liver, an increased serum bilirubin is a logical consequence. I doubt if jaundice means that she has gallstones or obstruction of her biliary tract, because obstruction of the bile ducts usually is accompanied by chills and fever — symptoms she lacked. I conclude she had a mesenteric infarction involving the small bowel. She may also have had a previous small embolus that gave her vascular ischemia and three months of abdominal symptoms. Finally, she had a rheumatic heart disease with mitral stenosis, decompensation, pleural effusion, and atelectasis with a possible pulmonary infarction.

Dr. Hay's Diagnosis

1. Mesenteric thrombosis possibly secondary to embolus, with infarction of small intestine.
2. Rheumatic heart disease with mitral stenosis.
3. Pleural effusion with atelectasis.

Comments

Dr. Wayne Chadbourn*

I was wondering if the patient had been on oral diuretics before admission.

Dr. Richard Reece

No, she received mercurial diuretics and had not been on Esidrix K.

Dr. Hay

I should have asked that question. Potassium in chlorthiazide diuretics has been established as a cause of small intestinal ulcers. This usually leads to the symptoms of a mechanical obstruction, not a silent abdomen.

Dr. Manuel Andrada**

His patient was on anticoagulant therapy. She might have bled into the bowel wall.

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*Pathologist, St. Barnabas Hospital.

**Chief Resident in Surgery, St. Barnabas Hospital.

Dr. Hay

Hemorrhage into the bowel wall is a possibility, but again this would cause localized obstruction with cramps and high-pitched bowel sounds.

Dr. Mork:

The x-rays show no thickening of the bowel wall or mass. Both are usually seen with intramural hematomas from anticoagulants.

Dr. Alfredo Arriola*

We saw a patient last year with a similar history. The patient had a history of congestive heart failure and had been on dicumarol. She developed abdominal pain, and we diagnosed an embolus with mesenteric infarction. When she was explored, it turned out to be due to periarteritis nodosa.

Dr. Hay

Rheumatoid arthritis and periarteritis nodosa are both auto-immune diseases, but in long-standing rheumatic heart disease, an arteritis can usually be discounted. This patient had no evidence suggesting a smouldering connective tissue disorder.

Dr. Harsharan Kaur*

I have seen two patients with heart disease who suddenly went into shock. In both, levophed was given to maintain blood pressure, but both died. Each had infarction of the bowel wall without thrombi in the vessel. Could this be a similar patient?

Dr. Hay

There have been many cases where patients on levophed developed gangrene of the bowel.[1] The patient's own epinephrine causes vasoconstriction of splanchnic and peripheral vessels, and levophed increases the constriction. As experience accumulates in treating cardiac shock, the question is being raised if levophed is doing more harm than good. Although it dilates the coronaries, it increases the peripheral vascular resistances, thereby causing more work by the heart.

Dr. Angilito Ramos*

I found a report of operative cases with symptoms of heart failure although the preoperative diagnosis was mesenteric infarction but the vessels contained no clots at operation or autopsy. The authors attributed the necrosis of the intestines to mesenteric spasm.[2]

Dr. Andrada

If you suspect mesenteric embolism or thrombosis but are not sure of your diagnosis, when do you operate?

Dr. Hay

In a patient with mitral disease, such symptoms as abdominal pain with distention, paralytic ileus, bowel obstruction, vomiting, passage of blood either by vomitus or by stool, or hypotension are all indications for oper-

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*Resident in Surgery, St. Barnabas Hospital.

Continued

ation. Laparotomy with a look at the intestine and palpation of the mesenteric vessels can save the patient's life. I had a resident who took out an elderly patient's appendix without looking at the remainder of the bowel or the vessels. The patient then died; he had an infarcted bowel. The resident then recalled that the bowel didn't bleed when he took out the appendix. Always look for the source of pain — don't do automatic surgery. It is better to find out whether it was a perforated ulcer, acute gallbladder, diverticulitis, twisted ovary, ruptured ovary, pancreatitis, or mesenteric block.

Pathological Discussion

Dr. Reece

We found a patchy, hemorrhagic necrosis of the stomach, duodenum, small bowel, and colon in the patient, and we believe it was secondary to heart failure. Hemorrhagic necrosis of the intestines is a common disease which has achieved popularity in the literature. In the last year seventy-five cases were reported from the Beth Israel Hospital in Boston, 31 cases from the Minneapolis Veterans Hospital, and 10 at the Lancaster Hospital in Lancaster, Pennsylvania.[3-5] In the report from the Beth Israel Hospital, Dr. Ming found 75 cases in 1535 consecutive autopsies — an incidence of nearly 5%. A review of this patient's lesions will illustrate the typical pathological picture.

The operation on April 10 was a small bowel resection. The provisional diagnosis before surgery was superior mesenteric embolism with infarction. As soon as he opened the abdomen the surgeon was confronted with a purple bowel distended with blood. The mesenteric vessels were collapsed but showed a feeble pulsation. The surgeon did not find a thrombus. He observed that the bowel wall bled briskly at all points where he cut into it. The pathologist, Dr. Chadbourn, described 16 feet of dusky hemorrhagic small bowel without any thrombi in the vessels. Microscopically, he saw an intact wall without any inflammation, but the mucosa showed hemorrhagic necrosis with extravasation of red cells in the lumen (Figures 3 and 4). No thrombi were found.

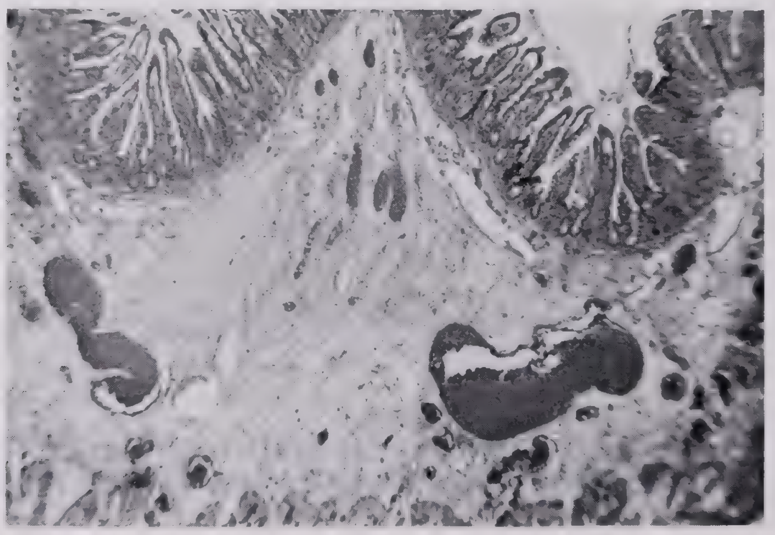

Fig. 3 — Photomicrograph of small intestine showing hemorrhagic necrosis of mucosa, edema of the submucosa, and dilated veins. (x35)

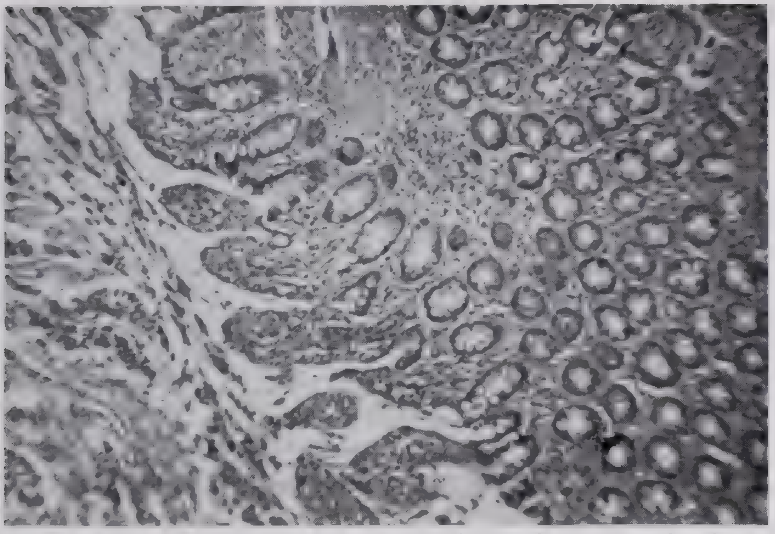

Fig. 4 — Photomicrograph of small bowel mucosa showing hemorrhagic villi and extravasation of red cells into the lumen. (x100)

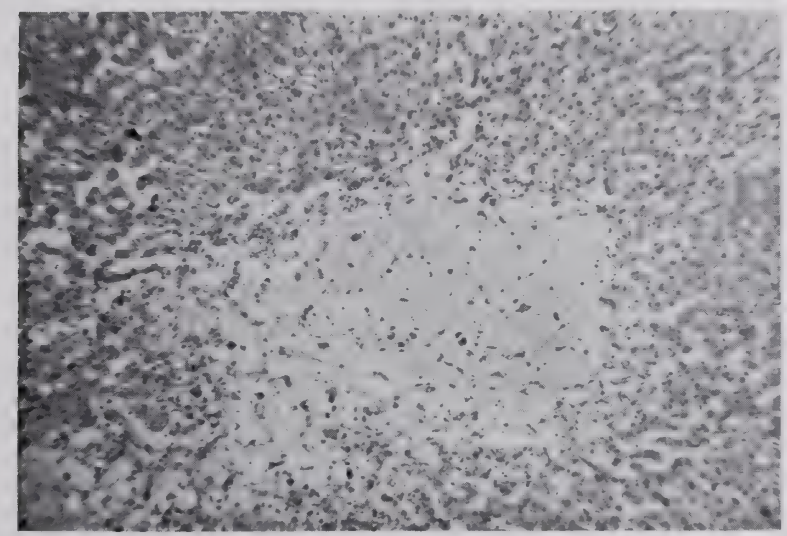

Fig. 5 — Photomicrograph of liver displaying extensive centrilobular necrosis. (x100)

Later at autopsy, the body was cyanotic and showed ankle edema and petechiae of the skin. The right pleural space was filled with hemorrhagic fluid. Both lungs were collapsed. The heart weighed 400 grams and showed a "fish-mouth" type of mitral valve, with large atria. There were no thrombi in the auricular appendages and no evidence of aortic insufficiency. The liver was mottled and showed severe centrilobular necrosis with neutrophils at the central zone (Figure 5). This probably accounts for her jaundice and her elevated prothrombin time because her liver was riddled with necrotic areas. The spleen was also enlarged and showed severe congestion and some early poorly demarcated infarcts with acute inflammatory reaction. The entire remaining gastrointestinal tract exhibited confluent hemorrhage of the mucosa.

Our final diagnoses were hemorrhagic necrosis of the gastrointestinal tract, rheumatic heart disease with mitral stenosis, and central hemorrhagic necrosis of the liver.

Continued

What is this disease complex of nonocclusive hemorrhagic necrosis of the bowel? First, a little history. In 1939 Penner and Burnham described 40 cases of necrosis in the bowel in which they found no thrombi.[6] Their paper was forgotten until 1954, when Wilson and Qualheim described 20 cases of a disorder simulating mesenteric infarction and occurring in individuals with chronic heart failure.[7] In the last six years a crescendo of reports have appeared,[2,8,9] and in the last year at least 116 cases have been reported of nonocclusive necrosis.[3-5]

Microscopically, changes are restricted to the mucosa, without necrosis or inflammation of the wall. The submucosal veins are distended with blood. Almost all patients have congestive heart failure, 80% are in shock, and 33% have gastrointestinal bleeding.[3] The common denominator in these patients seems to be a sharp decrease in the blood flow to the intestines secondary to vasospasm and with sludging in the splanchnic bed and venous distention. Digitalis toxicity increases failure and potentiates the syndrome.[9]

Signs and symptoms include abdominal distention, diffuse pain, vomiting, diarrhea, and decreased bowel sounds. In 60% of patients the symptoms last one day or less, but in the remainder the symptoms may be present for weeks or months.[3]

Dr. Hay

In animals with irreversible shock mucosal hemorrhage of the bowel is encountered. If the pancreatic duct is ligated to keep trypsin out of the lumen the animals tolerate more shock without an irreversible change. If antitrypsin agents are placed in the lumen of the bowel, a similar effect is achieved. Trypsin can be given either orally or by nasal tube.

Dr. Reece

A final comment on the chain of events. Patients in shock will perfuse their heart and brain to the exclusion of everything else. With profound heart failure intense spasm of all their mesenteric vessels results with shunting of the blood to the more vital centers. Because of the compensatory shunting mechanism, the bowel mucosa is deprived of blood and a conglomeration of microinfarcts results. The vessels of the small intestine, the arteries and the small bowel mucosa are extraordinarily vulnerable to anoxia.

Dr. Hay: This patient had heart block and marked systolic hypertension. Intestinal necrosis may have been the result of vasoconstriction in an attempt to save the vital organs.

Final Anatomical Diagnosis

Hemorrhagic necrosis of mucosa of gastrointestinal tract, patchy.

Centrilobular hepatic necrosis, severe.

Rheumatic heart disease, with mitral stenosis, visceral congestion, and right pleural effusion.

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3-9 May be secured from the C.P.C. Editor.

Grand Rounds

Nonocclusive Mesenteric Infarction of the Intestine

M. THOMAS STILLMAN, M.D.
Medical Resident

THERE ARE MANY causes of infarction of the intestine, among which are included mesenteric artery embolism or thrombosis, mesenteric vein thrombosis, and mechanical compression of these vessels or their branches. These causes may be grouped under occlusive vascular disease. There still remain the relatively few cases of intestinal infarction without demonstrable vascular occlusion. It is the purpose of this paper to present a case report to illustrate this phenomenon, discuss its varied aspects, and bring this entity to the attention of the clinician.

Clinical Syndrome

Many authors have reported various cases in which the bowel was implicated in the death of the patient. Marston[1] reviewed this subject and presented a useful diagram illustrating the various mechanisms of death in bowel ischemia (Figure 1). This paper will deal with that portion of the diagram leading to reduced mesenteric flow from nonocclusive or non-blocking mechanisms. It was not long ago that nonocclusive mesenteric infarction was first recognized as a definite clinical entity and referred to as pseudomembranous enterocolitis,[2] acute hemorrhagic enterocolitis,[3] acute hemorrhagic necrosis,[4] and hemorrhagic duodenitis.[5] The syndrome is now recognized as occurring in aged or chronically ill individuals with associated congestive heart failure, myocardial infarction, cardiac valvular lesions, and cardiac arrhythmias.

One of the first cases was reported in 1949,[6] that of a 73-year-old woman found to have a gangrenous small bowel without mesenteric vasculature occlusion. In 1951 Cohen[7] reported on a review of over 23,000 autopsy

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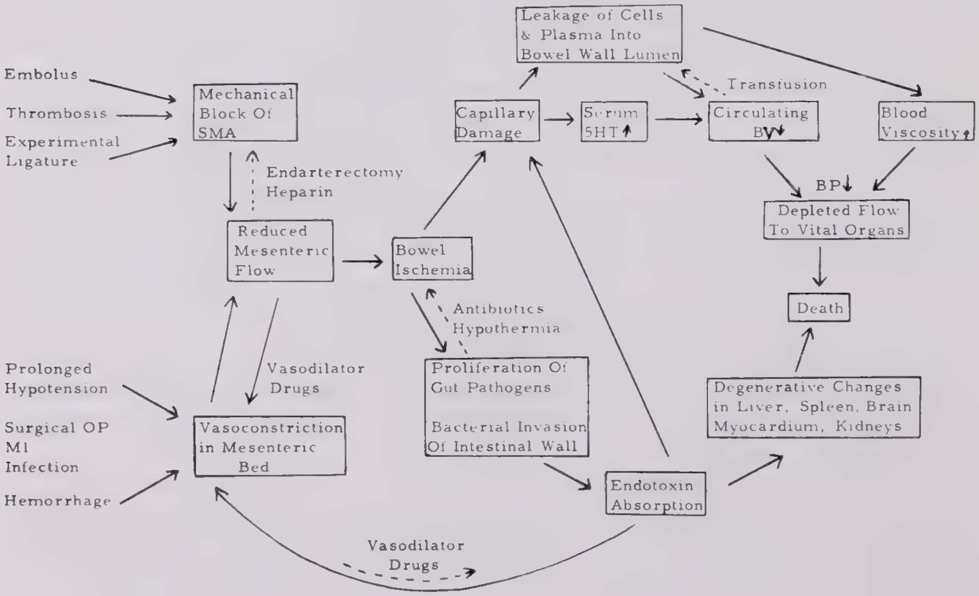
*Presented as a Medical Grand Rounds at Hennepin County General Hospital, February 16, 1966.

Continued

studies and found four cases of infarction of the stomach secondary to vascular occlusion. An incidental finding of a case involving infarction of the entire large and small bowel with no vascular occlusion was mentioned in a patient with severe right heart failure. The first report of the clinical syndrome best fitting our case was that by Wilson and Qualheim in 1954.[3] They observed 20 cases, described this syndrome and its pathologic picture and differentiated the various types of nonocclusive ischemic bowel syndromes. In 1956 Wilson and Block,[8] and Jenson and Smith,[9] described studies of mesenteric infarction. Wilson reported six out of 32 cases and Jenson reported 10 out of 51 cases of infarction in which no occlusion was found at autopsy. Both pointed out that the occlusion, either an embolus or thrombus, was probably not found or dislodged at postmortem examination. In 1958 Ende[10] studied six cases and emphasized the importance of congestive failure as an etiologic possibility. In 1960 Ming and Levitan[4] reported on the pathologic findings of this syndrome, and Hoffman and others[11] pointed out the importance of cardiac valvular lesions as a possible etiologic factor. Since 1960 there have been other studies contributing to the recognition of this clinical entity.[12-19]

Incidence and Mortality

The reported incidence of nonocclusive mesenteric infarction varies. Two of the above studies reported a 20 per cent[8,9] incidence in which no occlusion was found in cases of mesenteric infarction. Berger and Byrne[12] reported on 110 autopsy cases of massive bowel infarction not including mechanical disturbances such as volvulus, hernia, or intestinal obstruction. About 21 per cent of the cases showed no mesenteric vessel occlusion, and a review of these cases showed much similarity to our patient. Wilson and Qualheim[3] found an autopsy incidence of about 0.6 per cent in reviewing 3,400 autopsies of patients over 30 years of age in a six-year period. The incidence is probably even higher, for in addition to the occasional case



Leakage of Cells & Plasma Into Bowel Wall Lumen
Embolus
Thrombosis
Experimental Ligature
Mechanical Block Of SMA
Transfusion
Capillary Damage
Serum 5HT↑
Circulating BV↓
Blood Viscosity↑
Endarterectomy Heparin
BP↓
Depleted Flow To Vital Organs
Reduced Mesenteric Flow
Bowel Ischemia
Death
Antibiotics Hypothermia
Prolonged Hypotension
Vasodilator Drugs
Proliferation Of Gut Pathogens
Bacterial Invasion Of Intestinal Wall
Degenerative Changes in Liver, Spleen, Brain Myocardium, Kidneys
Surgical OP
MI
Infection
Vasoconstriction in Mesenteric Bed
Hemorrhage
Endotoxin Absorption
Vasodilator Drugs

*From Marston, The Lancet, 2:365, 1962.

Figure 1

that recovers there are cases that do not go on to autopsy study.

Usually the disease is rapidly fatal. The average duration of life when the exact onset can be determined has been reported to be from one to five days.[3]

Diagnosis

This disorder is generally found in the elderly, chronically ill patient. Most studies report a mean age of about 70 years, and there does not seem to be a predominance of one sex over the other. A common associated condition is that of chronic cardiovascular disease manifested primarily as congestive heart failure. The type of cardiac disease varies. Wilson and Qualheim[3] report 20 cases of this syndrome with 85 per cent having chronic heart disease. The predominant type was arteriosclerotic and/or hypertensive heart disease (Table 1). The frequent occurrence of congestive heart

TABLE 1*
Summary of Clinical Features of Acute Hemorrhagic Enterocolitis

Cases			20
Sex, Race, Age, Season of Onset:			
Male		9	
Female		11	
White		14	
Negro		6	
Age over 60 years		16	
Age under 60 years		4	
Winter admissions (October-March)		7	
Summer admissions (April-September)		13	
Association With Heart Disease:			
Chronic heart disease		17	
Arteriosclerotic and/or hypertensive	16		
Rheumatic valvular	1		
Chronic congestive heart failure, history	15		
Chronic congestive heart failure, at onset	12		
No heart disease		3	
Abdominal Signs and Symptoms:			
Abdominal pain		11	
Abdominal tenderness		13	
Abdominal distention		12	
Diarrhea		15	
Bloody diarrhea	8		
Vomiting		7	
Bloody vomiting	3		
Clinical Diagnosis:			
Mesenteric thrombosis		7	
Massive gastrointestinal bleeding, site undetermined		3	
Incarcerated femoral hernia		1	
Acute hemorrhagic enterocolitis		1	
No serious intra-abdominal disease considered present		8	
Deaths			20

*From Wilson and Qualheim, Gastroenterology, 27:432, 1954.

Continued

failure, either chronic or acute, is also demonstrated in this report. This is substantiated by its presence in 100 per cent of cases reported by Ende,[10] 70 per cent of the cases reported by Ming and Levitan,[4] 90 per cent of the cases reported by Berger and Byrne,[12] 75 per cent of the cases reported by Kligerman and Vidone.[18] Musa[17] reported on 31 cases of intestinal infarction without mesenteric vascular occlusion. About 50 per cent of his cases had atherosclerotic and/or hypertensive heart disease and 30 per cent had rheumatic heart disease (Table 2). A number of studies include the presence of valvular lesions, the most prominent being aortic insufficiency as in the case study. About 30 per cent of the patients reported by Musa[17] had aortic insufficiency (Table 3). Hoffman and others[11] reported five cases of intestinal infarction associated with aortic insufficiency, 80 per cent of these cases having a syphilitic etiology. Other studies demonstrate this association.[20] The presence of arrhythmias has been demonstrated in cases of nonocclusive infarction of the bowel.[21] The predominant type has been atrial fibrillation. Musa[17] found atrial fibrillation present in about 40 per cent of his cases (Table 4). The presence of new or old myocardial infarction ranged from about 20 to 30 per cent of the cases.[17,18] Finally the presence of shock was common to many of the reported cases, but its exact relationship to the onset of symptoms of infarction of the bowel is not easily determined.

Signs and Symptoms

The signs and symptoms are essentially non-specific with reference to the gastrointestinal tract. They include abdominal pain, tenderness, disten-

TABLE 2*
Type of Heart Disease

Type	Cases
	No.
Atherosclerotic	12
Hypertensive	1
Hypertensive and atherosclerotic	2
Rheumatic	10
Luetic	1
Cor pulmonale	2
Congenital	1
Senile aortic ectasia	1
No heart disease	1

*From Musa, Annals of Int Med 63:788, 1965.

TABLE 3*
Type of Valvular Lesions

Type	Cases
	No.
Aortic insufficiency	10
Aortic stenosis	7
Mitral insufficiency	6
Mitral stenosis	6
Tricuspid insufficiency	1

*From Musa, Annals of Int Med 63:788, 1965.

TABLE 4*
Cardiac Rhythm

Type	Cases
	No.
Sinus	14
Atrial fibrillation	13
Wenkebach	1
Atrial flutter	1
Nodal	1
Atrial tachycardia	1

*From Musa, Annals of Int Med 63:788, 1965.

tion, diarrhea (sometimes bloody), and vomiting (sometimes bloody). Their frequency is presented in Table 1. The presence of bowel sounds is highly variable as is the degree of fever. Usually because of the association of heart disease and non-specificity of abdominal findings, the abdominal problem is minimized in evaluation of the patient.

Laboratory Findings

Although the laboratory findings are variable, there seem to be certain constant findings. A leukocytosis up to 25,000 WBC was a frequent finding. A hemoglobin greater than 13 grams was reported in 90 per cent of the cases of Ming and Levitan.[4] Musa[17] reported albuminuria present in more than 90 per cent of the cases. He also reported a BUN greater than 25 milligrams per cent in more than 60 per cent of the cases. The laboratory findings in our case are consistent with the above reported data. Except for the radiologic evidence of non-obstructive ileus, there are no definite x-ray signs. Berger and Byrne[12] suggest that the presence of dilated small and large bowel patterns with the absence of air beyond the mid-transverse colon may be a radiologic sign. The diagnosis is not easily made, as demonstrated by the relatively low incidence of correctly reported diagnoses prior to autopsy.

Pathology

In fact, it is primarily on a pathologic basis[3,4,18] that this entity is separated from other necrotic lesions of the bowel.

TABLE 5*
Summary of Pathologic Features of Acute Hemorrhagic Enterocolitis

Cases	20
Distribution of Intestinal Lesions:	
Esophagus	0
Stomach	2
Duodenum	6
Jejunum	16
Ileum	16
Colon	17
Rectum	8
Stomach and duodenum only	1
Small intestine only	2
Large intestine only	1
Small and large intestines	16
Lesions:	
Mucosal hemorrhage	20
Submucosal edema	20
Mucosal ulceration (macroscopic)	10
Peritonitis, focal	2
Liver abscess, acute, secondary	1
Primary Cause of Death:	
Acute hemorrhagic enterocolitis	14
Congestive heart failure	4
Bronchiectasis and bronchopneumonia	1
Encephalomalacia, extensive	1

*From Wilson and Qualheim, Gastroenterology, 27:433, 1954.

Continued

Gross

The gross findings include a wide distribution of lesions but are most frequently localized in the distal half of the small intestine and proximal half of the colon. Some cases include the entire intestine from pylorus to anus, as in our case. The serosal surface is dark, purplish, and appears congested, and the presence of a thickened wall is usually due to the submucosal layer. The lesions occur in patches or segments unrelated to a particular vascular pattern as seen in occlusive vascular infarction. The lumen is often filled with a dark, bloody fluid. No mesenteric vascular occlusion is evident (Table 5).

Microscopic

A constant microscopic pattern is present. The early picture is that of hemorrhagic mucosa with blunted or edematous villi that become necrotic at the ends. The mucosal and submucosal vessels are dilated and engorged. There is no inflammatory reaction present early in this process. Later, the above is present in a greater degree and the only evidence of inflammation is in the areas of mucosal ulceration. The distincitve features of the pathological picture include widespread, often patchy, necrotic and hemorrhagic lesions limited to the mucosa and submucosa with little or no inflammatory reaction present.

Pathogenesis

The pathogenesis of nonocclusive mesenteric infarction is difficult to determine and remains somewhat vague.

Congestive Heart Failure with Increased Venous Pressure

The presence of congestive heart failure has been offered as a cause for infarction of the bowel. Ende[10] reported on bowel infarction occurring in cases of congestive heart failure. The resulting increase in venous pressure and liver congestion was thought to be a precipitating factor. Selkurt and Johnson[22] studied the effects of increased portal venous pressure upon the mesenteric circulation, and they point out that because the venous drainage of the intestine passes through the liver, the blood volume of the intestine is dependent upon the vascular resistance of the liver. By measuring blood flow through the portal veins of dogs as well as measuring weights of intestine, they were able to show an increase in mesenteric arteriolar vascular resistance resulting from increases in portal venous pressure.

Local Vasoconstriction

By the use of denervation as well as adrenergic blocking agents, they[22] proposed the presence of a local reflex or a direct myogenic response of smooth muscle within blood vessels. Increased vascular intraluminal pressure leads to vasoconstriction and secondary bowel ischemia. Paul and others[23] reported the presence of venous dilatation, capillary engorgement and edema of the intestinal wall in reviewing 50 cases of congestive heart failure. They did not report any cases of frank infarction. Thus it has been concluded that congestive heart failure itself does not cause intestinal infarction, but the secondary liver congestion and probable resulting additional vasoconstriction of the vessels in the splanchnic bed cause enough ischemia to result in infarction.

Arrythmia

Since arrhythmias are often associated with this syndrome, they have been reported as a possible etiologic factor. Irving and Corday[24] showed in dogs the effect of arrhythmias on mesenteric blood flow. Atrial fibrillation, commonly present in patients with this disease entity, reduced the flow an average of 34 per cent, with prompt return of flow to normal upon cessation of the arrhythmia.

Shock

Shock has long been proposed as a possible etiology in nonocclusive bowel infarction. A basic concept proposed by Fishberg,[25] the theory of selective vasoconstriction and redistribution of blood, operates during clinical shock. Irving and Corday[24] point out that a large amount of blood within the mesenteric circulation may be shunted to more vital organs such as the brain or heart, this quantity representing about 15 per cent of the cardiac output. They refer to the mesenteric circulation as the "homeostatic watchdog of the systemic circulation." Corday and Williams[26] further demonstrate this preferential vascular treatment of the brain and heart with resultant ischemic changes in the intestine as response to shock and the use of vasopressor drugs in dogs. In a unique experiment involving the isolation of loops of bowel in dogs, Corday and others[27] were able to show that angiospasm of the arterioles within the intestinal wall was the responsible factor in producing ischemia occurring during hemorrhagic shock and during the use of vasopressor drugs. The authors propose that this is the mechanism for hemorrhagic necrosis reported as following myocardial infarction, cardiac arrhythmias, and congestive heart failure. Lillehei[28] discusses the intestinal factor in irreversible hemorrhagic shock. He demonstrated that by perfusion of the intestine during hemorrhagic shock in dogs, the animals recovered upon retransfusion. The non-perfused dogs went on to die following copious amounts of bloody diarrhea. At autopsy the bowel showed severe mucosal congestion and necrosis. Lillehei also showed that by use of Eck fistula dogs, portal congestion is not the direct cause of bowel lesions secondary to shock conditions. In Musa's series[17] clinical shock was present in about 50 per cent of the cases, and it preceded the abdominal pain in only about 30 per cent of the cases. He felt that in man, shock was a factor in bowel infarction only when pre-existing disease (mainly heart disease) was present.

Immunological Reaction

Another factor considered as etiologic is an immunological or hypersensitive reaction.[13,15,29,30] Levine[15] reported a case of intestinal infarction without the presence of heart disease and demonstrated similar lesions in the intestine of guinea pigs by injection of rabbit Forssman antisera. The mechanism proposed with that Forssman antigen on the endothelium of blood vessels served as a focus for an antigen-antibody reaction, resulting in endothelial damage with increased permeability leading to edema, stasis, hemorrhage, and necrosis of the bowel wall. The presence of necrotizing arteriolitis involving terminal mesenteric vessels has been reported.[30] These lesions are similar to those seen in collagen diseases. An arteritis secondary to high doses of vasoconstrictor agents has also been reported.[29]

Neurogenic

Palmero and others[31] demonstrated that denervation of the abdominal

Continued

viscera leads to improved mesenteric blood flow during shock, thus implicating a neurogenic etiology in infarcted bowel lesions, and also that endotoxins produce shock indirectly via the nervous system. These authors felt that endotoxin stimulates the sympathetic nervous system to excessive activity leading to damage of the reticular endothelial system and failure to detoxify the endotoxin. The presence of endotoxin can produce the lesion of hemorrhagic mucosal necrosis.

Other Factors

Gazes and others[16] showed with hemodynamic studies that digitalis exerts constrictive effects on the liver, resulting in portal splanchnic venous congestion and a possible mechanism for bowel infarction.

Before we leave the subject of pathogenesis, one more theory should be noted. Hoffman and others[11] discuss the law of La Place. This relates tension in the wall of a blood vessel to the size of the vessel and the pressure within. Smaller vessels have limited stability. As the pressure within a smaller vessel decreases, its tone within the walls increases to a point at which there is complete closure of the vessel. Thus there are critical closing pressures below which a small arteriole within the intestine will become unstable and close. This can lead to edema, hemorrhage, anoxia, and necrosis without thrombosis or embolization. This has been proposed as a mechanism in aortic insufficiency.

Differential Diagnosis

Clostridium Welchii and Pseudomembranous Enterocolitis

The clinician is faced with the differential diagnosis of an acute abdomen, except that the abdominal symptoms in this syndrome are initally mild and often overlooked. It is not until late in the course that the clinician recognizes the associated presence of possible intestinal pathology. One entity known as enteritis necroticans is an enterocolitis that also has an abrupt onset, blood diarrhea, early circulatory collapse, and rapid progression to death. It is thought to be due to a Clostridium welchii infection of the bowel.[32] Nonocclusive mesenteric infarction differs in that previously well individuals are usually not affected and a causative organism is not isolated. The pathologic picture differs in that there is a lack of inflammation with involvement of only the mucosa and submucosal layers in the infarction syndrome. The pathologic picture as well as the presence of hemorrhage separates this entity from the pseudomembranous enterocolitis seen postoperatively or following the use of broad-spectrum antibiotics.

Occlusive Infarction

The real difficulty arises in distinguishing nonocclusive infarction from occlusive infarction, and this is usually not resolved until the patient undergoes surgical exploration or is studied at autopsy. Glotzer and Shaw[21] point out the importance of recognition of the associated conditions with nonocclusive infarction syndrome referred to earlier in the paper. In a review of 31 cases of massive bowel infarction they found nine cases without vascular occlusion. In the nonocclusive group, atrial fibrillation and other major arrhythmias were present in 78 per cent of the cases as opposed to 47 per cent of the cases in the occlusive group. Congestive failure was present in 67 per cent of the cases of nonocclusive and only 31 per cent of the cases of occlusion.

Treatment

Supportive Care

There is very little available in the way of definitive treatment for this entity. The importance lies in its recognition and vigorous treatment of the precipitating or associated conditions such as cardiac arrhythmias or congestive heart failure. Supportive care includes intestinal intubation to reduce distention, and the use of intravenous fluids. Most authors recommend the use of antibiotics to reduce the number of endotoxin-producing bacteria. Berger and Byrne[12] reported the average survival time of patients receiving no antibiotics or only a single dose to be 3.2 days. Those given more than a single dose lived an average of 7.5 days after the onset of symptoms.

Splanchnic Block

An excessive amount of vasopressor agents should be used cautiously in view of the findings noted earlier in the paper. Laufman[33] reported the beneficial effect of injections of procaine hydrochloride into the mesentery of strangulated bowel along with intravenous use of papaverine. Periarterial sympathectomy and continuous splanchnic block have been used with markedly varying results. It is generally accepted that these patients represent poor surgical risks as they are unlikely to have a surgically correctable lesion. If frank infarction is not found, nothing definitive can be done; if infarction is present, multiple segment involvement makes resection difficult or not feasible.

Summary

The syndrome of nonocclusive mesenteric infarction of the intestine occurs in elderly chronically ill patients with associated conditions such as myocardial infarction, cardiac arrhythmias, cardiac valvular lesions, and congestive heart failure. The mortality rate is very high. The signs and symptoms may include abdominal pain, tenderness, and distention with bloody diarrhea or vomiting. Laboratory and x-ray findings are not specific and the diagnosis is seldom made early in the course of the disease. The pathologic picture has been described in detail and the distinctive features include widespread involvement with hemorrhagic non-inflammatory lesions limited to the mucosa and submucosal layers. Many possible etiologic factors have been discussed, the exact mechanism remaining obscure. The mesenteric circulation serves a homeostatic function in that it shunts blood to more vital organs during clinical shock, often at the expense of the gastrointestinal tract. The treatment is essentially supportive and the importance lies in early recognition of the disease entity along with adequate treatment of the associated conditions.

Case Report

History

A 70-year-old white male was admitted on 9/29/65 for evaluation of shortness of breath and abdominal pain. The patient had been resting at home when he became acutely dyspneic, cyanotic, and markedly diaphoretic. He noted some abdominal cramping associated with this episode. He did not lose consciousness. The past medical history was significant in that he was hospitalized five years prior to admission for a myocardial infarct. He was again hospitalized eight months prior to admission for acute congestive failure and was told he had valvular heart disease. He was maintained on a digitalis preparation and a thiazine diuretic. Except for increasing exertional dyspnea during the week prior to admission, he was doing quite well.

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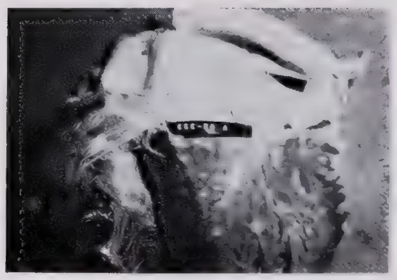

Fig. 1 — Stretched commissures of the aortic valve resulting in aortic insufficiency, high coronary ostia (pointer).

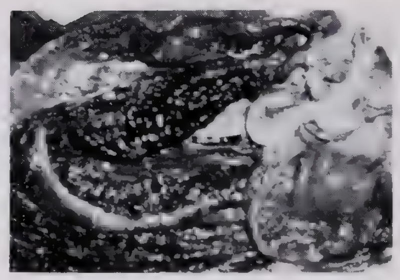

Fig. 2 — Congested, hemorrhagic infarcted bowel.

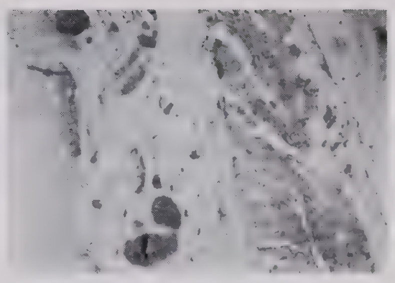

Fig. 3 — Necrotic mucosa, edematous submucosa with dilated vessels, minimal inflamation.

Physical Examination

The patient was an elderly man, cyanotic, dyspneic, diaphoretic, with moderate abdominal pain. Blood pressure was 180/90, pulse 120 and irregular. The presence of congestive failure was evident by distended neck veins, bilateral rales in the lungs, and a gallop rhythm. An apical systolic murmur and atrial fibrillation were present, but no diastolic murmur was detected. There was minimal abdominal tenderness upon palpation; there was no organomegaly; the bowel sounds were within normal limits and there was minimal pedal edema present.

Hospital Course

The initial EKG showed a rapid atrial fibrillation, left ventricular hypertrophy, and probable old anterolateral myocardial infarct. A chest film showed marked cardiomegaly. The patient's congestive failure responded well to increased digitalization, diet, diuretics, and bed rest; but on the second hospital day he developed increased abdominal pain, hypoactive bowel sounds, and grossly bloody diarrhea. Sigmoidoscopy was negative to 15 centimeters. Initial CBC showed a hemoglobin of 15.8 gm., WBC of 20,800 per cu. mm. with 91 per cent neutrophils, and hematocrit of 48 per cent. During hospitalization, the hemoglobin remained stable between 14 and 15 grams. The BUN rose from 52 to 89 mg. per cent. ESR rose from 1 to 26 mm. per hour, SGOT from 36 to 97 units. A serum amylase was 57 units. A sputum culture showed a mixture of organisms with E coli predominant. The patient was placed on penicillin and streptomycin. A blood culture was negative. The patient's bloody diarrhea persisted; he became febrile and progressively hypotensive, and died on the fourth hospital day.

Autopsy

The autopsy study revealed the following: the heart weighed 500 grams and there was a scar present in the anterior aspect of the lateral ventricle. There was a dilatation of the ascending aorta with stretching of the commissures of the aortic valve, resulting in aortic insufficiency. The liver showed acute and chronic passive congestion. Gross examination of the gastrointestinal tract revealed a purplish appearance of the entire ileum and large bowel which appeared congested, hemorrhagic, and infarcted. Microscopic examination of the intestine showed scattered mucosal hemorrhage and necrosis with minimal inflammation. The submucosa was edematous and dilated vessels were present. The mesenteric vessels showed *no occlusion.* The diagnosis was congestive heart failure and aortic insufficiency with secondary nonocclusive infarction of the intestinal tract.

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11-33 May be secured from the Grand Rounds Editor.

Advances

Antibacterial Management of Infections Due to Gram-Negative Bacilli

Part II. Use of the Tetracyclines, Chloramphenicol, Polymyxin B, Colistin, Cycloserine, and Paromomycin*

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Rochester, Minnesota

The Tetracyclines

INTRODUCTION OF tetracycline (Achromycin, Tetracyn, Panmycin KM, Polycycline) largely supplanted use of oxytetracycline (Terramycin) and chlortetracycline (Aureomycin), but the three agents are interchangeable for clinical use. Demethylchlortetracycline (Declomycin) is said to maintain higher blood levels longer than do the older drugs, but this is disputed. Pyrrolidinomethyl tetracycline or Rolitetracycline (Syntretin, Velacycline), when given by intramuscular injection, probably provides higher serum levels than the parent drug; the drug also can be given intravenously. There are other derivatives currently being investigated, such as 6-methyleneoxytetracycline, known as methacycline (Rondomycin) and given orally.

Indications for Use

As aforementioned, the tetracyclines along with streptomycin are used in such conditions as pneumonia due to *Klebsiella pneumoniae,* infection due to *Vibrio fetus* and brucellosis. In infections due to the tribe Mimeae a tetracycline along with kanamycin, polymyxin B, or colistin may be advisable. The tetracyclines are used, usually as single agents, in *actinomycosis, psittacosis, rickettsial diseases, pneumonia due to Mycoplasma pneumoniae,* and the less common venereal diseases: *lymphopathia venereum, granuloma inguinale, and chancroid.* In treponemal and gonococcal infections, the tetracyclines are useful in patients allergic to penicillin. In enteric amebiasis, the tetracyclines are used by some workers as adjuvants to other amebicides, but not in hepatic amebiasis. The tetracyclines are also used in patients with mucoviscidosis and other forms of chronic pulmonary disease. Favorable reports from tetracycline therapy are described in some cases of *Whipple's disease, tropical sprue, malabsorption associated with intestinal scleroderma, and diabetic diarrhea.* Tetracyclines are not used in infections due to beta-hemolytic streptococci or pneumococci unless in-vitro tests indicate susceptibility.

Side Effects

Nausea, vomiting, and looseness of the stools may occur on oral use of these drugs. However, when frank diarrhea results, staphylococcal enteritis should be excluded. Superinfection may be due to other organisms such as *Candida, Proteus,* and *Pseudomonas* and result in pneumonia, bacteremia, etc.

Continued

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*See Part I Minnesota Med 49:835, 1966.

**Mayo Clinic and Mayo Foundation: Section of Medicine.

Drug fever, rashes, glossitis, stomatitis, and pruritus perenea are other untoward effects. Anaphylaxis, hematotoxicity, and pericarditis are rare toxic reactions.

When a tetracycline is added to solutions employed in peritoneal dialysis, the possibility of an untoward effect of the antibiotic should be considered. In markedly azotemic patients peak levels in serum, approaching the therapeutic range, may be reached within 24 hours.

The tetracyclines are not detectable in most normal tissues 12 to 24 hours after their administration is discontinued, but they may be retained indefinitely in mineralized tissues. Pigmentation and faulty enamel formation of children's teeth may follow use of the drugs either by the mother in late pregnancy or by the child in early life. Initially, the pigmentation is bright yellow but turns brownish with increasing age; exposure to light may intensify the pigmentation.

The tetracyclines are also retained in bone. If a tetracycline is given at a specific time before bone sampling, the amount of cortical bone formed between labeling and sampling can be measured by microfluorescence. The question has been raised whether deposition of the drugs in bones might inhibit their linear growth in premature infants, as has occurred in experimental animals. The drugs may be taken up by neoplastic bone and may have potential use in determining the level of amputation in osseous tumors.

Fluorescent Complex

Tetracyclines, excreted by the kidney and the hepatobiliary system, may be combined with calcium-containing urinary and biliary calculi to produce a fluorescent complex. Intermittent administration of a tetracycline to subjects prone to formation of urinary calculus may help determine the rate of growth of such stones, and also aid in evaluating regimens designed to prevent formation of calculi.

After prolonged tetracycline therapy, fluorescence of the nails may be demonstrable, and rarely can discoloration and onycholysis* be seen by the naked eye.

The affinity of tetracyclines for some types of malignant tissue, with fluorescence of the drug evident on exposure of the specimen to ultraviolet light, continues to be investigated in the hope that reliable diagnostic procedures will evolve. Patients given a tetracycline and then cystoscoped under ultraviolet light may be found to have malignancies of the urinary bladder, not evident on conventional cystoscopy. In the diagnosis of gastric carcinoma, testing of gastric washings for cells having tetracycline fluorescence may complement conventional cytology. Similar testing of duodenal fluid in patients suspected of having cancer of the pancreas or biliary tract is being investigated. Fluorescence may also help identify malignant cells in pleural and ascitic fluids. It is to be stressed, however, that these and allied procedures are largely investigational and that both false-positive and false-negative results are being encountered.

Accumulation in Damaged Tissue

In experimental animals, a tetracycline tends to accumulate in damaged but still viable myocardial tissue, particularly along the border of an infarcted area. In the living animal, a tetracycline tagged with iodine-131 is administered, and the radioactivity is measured via gammagraphy or scintillography. It is hoped that such investigation will lead to more precise identification of myocardial infarction in man.

Antianabolic Effects

The tetracyclines produce antianabolic effects that may have clinical significance in patients with reduced renal function. Negative nitrogen balance, increased urinary loss of such substances as sodium and riboflavin, increased azotemia, hyperphosphatemia, acidosis, and loss of weight may occur.

Hepatotoxicity

Fatal liver disease may occur in persons given excessive amounts of a tetracycline. Pregnancy, underlying hepatic disease, conjoint use of other hepatotoxic drugs, and impaired renal function increase the chances of hepatotoxicity. Most problems have resulted when more than 2 gm/day have been given intravenously, but the duration of therapy as well as the daily dose should be minimized when the drugs are given by any route. Jaundice, azotemia, acidosis, gastrointestinal bleeding, and hypotension may precede death. In doubtful cases, the serum concentration of the drug should be maintained at less than 15 μg/ml.

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*See Test Your Word Score Page 943.

Photosensitivity, manifested by marked erythema and sometimes edema, is more often associated with demethylchlortetracycline therapy but has occurred after chlortetracycline, oxytetracycline, or tetracycline has been used.

A tetracycline, especially when administered intravenously, may interfere with blood coagulation; such findings as increased clotting time, decreased plasma prothrombin activity, lowered prothrombin consumption, and retarded thromboplastin generation may occur.

*Fanconi's Syndrome**

A reversible Fanconi's syndrome can result from ingestion of outdated or degraded tetracycline. Unexplained vomiting, dehydration, muscle weakness, polydipsia, polyuria, glycosuria with a normal blood sugar, or metabolic acidosis indicates the reaction; proteinuria, acetonuria, aminoaciduria, potassium depletion, and loss of calcium and phosphate also occur. Bence-Jones proteinuria has occurred. Aminoaciduria may persist after other alterations disappear. Lethargy may progress to coma. Gait disturbances may last several months. Packaging of the tetracyclines with alpha-lactose monohydrate may delay degradation of the drugs.

An isolated defect of renal tubular function, manifested by polyuria and hyposthenuria, following ingestion of demethylchlortetracycline has been described.[1] This example of so-called nephrogenic diabetes insipidus appears to be a reversible effect of the intact drug and unrelated to excessive dosage.

Increased Intracranial Pressure

With full therapeutic doses of a tetracycline in infants, increased intracranial pressure with bulging fontanels has been observed but has disappeared on cessation of treatment.

Dosage

In serious infections, 2 gm/day of a tetracycline are given orally in four divided doses; occasionally 3 gm. are given. As aforementioned, it is disputed whether smaller doses of demethylchlortetracycline suffice. A film-coated tablet of demethylchlortetracycline in amounts of 300 mg. has been marketed with the claim that, when taken every 12 hours, blood concentrations of the drug are similar to those after use of 150 mg. in an uncoated tablet every six hours. On an investigational basis, 150 mg. of methacycline has been given four times daily for as long as eight weeks. Concomitant administration of antacids and foods, especially those of a high calcium content, impairs gastrointestinal absorption.

Oxytetracycline or tetracycline in 100-mg. doses intramuscularly every six hours or 200 mg. every eight hours may be given. Also available is a preparation of oxytetracycline, which can be given intramuscularly in amounts of 250 mg. every 12 hours. As much as 500 mg. of chlortetracycline, oxytetracycline, or tetracycline can be given intravenously every eight to 12 hours. Rolitetracycline is given intravenously or intramuscularly in amounts of 250 mg. once or twice daily. The instillation of the tetracyclines into body cavities is to be avoided because of the irritating chemical properties of these drugs.

Chloramphenicol

Chloramphenicol (Chloromycetin) currently appears to remain the drug of choice against typhoid fever and is employed in certain staphylococcal infections and sometimes in infections due to Enterobacteriaceae. Because of its comparative ability to permeate the central nervous system, it is useful in selected cases of infection of the central nervous system, such as influenzal meningitis.

Continued

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*See Minnesota Med 47:842, 1964.

Typhoid Fever

In cases of typhoid fever, a total of 45 gm. is given during a period of 14 days; some workers also give streptomycin for the first five days. Cortisone is given only to patients with severe pyrexia and toxicity. The 20% of patients who relapse are given a second course of chloramphenicol. The over-all mortality rate is less than 5%. As a generalization, chloramphenicol is not very effective in inducing permanent cures among chronic typhoid carriers; other drugs are often preferred.

Coincident with the declining rate of typhoid fever in the United States, an increase in other *Salmonella* infections has occurred. The natural habitat of these organisms is the gastrointestinal tract of animals and man, and the major sources of human infection are animals and their products, especially poultry and livestock. Many outbreaks occur after use of contaminated egg or egg products. Of the more than 800 known species of *Salmonella* organisms, the most common pathogen in human infection is *S. typhimurium*. Next, in decreasing order of frequency, are *S. thompson, S. newport, S. enteritidis,* and *S. heidelberg*. Clinical manifestations range from an asymptomatic carrier state to fulminating bacteremia; the latter cases are most commonly due to *S. choleraesuis*. Patients having certain underlying conditions such as sickle-cell disease, liver disease, and Hodgkin's disease may thereby be predisposed to *Salmonella* infection. Tetracycline, ampicillin, and other drugs may be more effective than chloramphenicol in systemic infections, and nonabsorbable agents like neomycin, kanamycin, paromomycin, colistin and polymyxin B, given orally, are often preferred in gastroenteritis derived from *Salmonella* organisms.

When chloramphenicol is given orally, sometimes a loading dose of 2 to 3 gm. precedes the regular administration of 500 mg. every four hours. In patients unable to accept the drug orally, 0.5 to 1 gm. of chloramphenicol sodium succinate is given intramuscularly or intravenously every six to 12 hours.

Sequelae

Aplastic anemia, thrombocytopenia, and granulocytopenia have occurred after both short-term and prolonged chloramphenicol therapy but rarely have complicated its local use, as may happen with use of ocular solutions. Regular studies to detect eosinophilia, leukopenia, anemia, thrombocytopenia, reticulocytopenia, and rising serum iron levels should be carried out. Hematotoxicity may represent an accentuated normal response to the drug, since mild reversible changes are not rare, and large doses given for prolonged periods will cause maturation arrest in a majority of subjects. However, in certain individuals, hypersensitivity probably contributes partially to the drug's hematotoxicity. Hematotoxicity is more frequent in Caucasian girls less than 12 years old. Some recent work indicates that 100 mg. of L-phenylalanine/kg. of body weight per day given orally may ameliorate the hematotoxicity.[2]

Other hematotoxic drugs include the sulfonamides, ristocetin, and less frequently streptomycin and the tetracyclines. Penicillin G, especially when given in large amounts for prolonged periods, rarely has caused anemia, evidently reflecting immune erythrocytic destruction.[3] Novobiocin, griseofulvin, methicillin, oxacillin, colistin, cephalothin, and lincomycin have caused transient leukopenia. Actually, all antibacterial agents have been accused of hematotoxicity on occasion, but contentions against the others are difficult to verify.

The fatal *"gray syndrome"* may occur in infants given chloramphenicol. Anorexia, abdominal distention, lethargy, flaccidity, hypothermia, respiratory distress, and "gray cyanosis" may reflect excessive concentration of the drug because of deficiencies of drug conjugation and excretion due to immature enzyme systems in the infant.

A *"typhoid shock"* syndrome occurs after the drug is used in typhoid fever; the shock, presumably caused by excessive release of endotoxin, resembles so-called bacteremic shock due to other gram-negative bacilli.

Chloramphenicol, streptomycin, and isoniazid are three antimicrobial drugs that may cause optic neuritis. The mechanism of the neuropathy may concern drug-induced pyridoxine deficiency.

Other untoward effects include stomatitis, glossitis, candidal superinfection, rashes, fever, and, on oral use, gastrointestinal irritation.

Polymyxin B

Polymyxin B (Aerosporin) is mainly used against *Pseudomonas* organisms but also is active against *Escherichia coli,* and the *Klebsiella-Aerobacter, Salmonella,* and *Shigella* groups. The drug is essentially lacking in anticoccal effect.

In certain gram-negative bacillary infections such as endocarditis or meningitis, conjoint use of other agents such as a tetracycline or chloramphenicol is considered.

Polymyxin B alone, and together with neomycin, has been administered orally to patients having enteritis from *Salmonella* or *Shigella* organisms; neither drug is well absorbed by the oral route.

A 25 to 50-mg. dose of polymyxin B is given intramuscularly every six to eight hours. Rarely, 50 to 100 mg. is given intravenously once or twice daily. In the azotemic patient, a single intramuscular dose given every two to four days may suffice. The drug is also administered intrathecally, intraocularly, and intrapleurally in doses of 1 mg. Polymyxin B has been given via inhalation, by aerosol directly into a tracheostomy tube, and topically to the ear, nose, and skin.

Untoward effects of polymyxin B include nephrotoxicity, pain on intramuscular injection, fever, flushing, pruritus, superinfection, acroparesthesia, cerebellar ataxia, headache, and a curare-like effect.

Colistin

Colistin differs from polymyxin B in only one of its amino acids and in the configuration of the molecule. Colistin sulfate is used orally while colistin methanesulfonate or colistimethate (Coly-Mycin) is the form used parenterally. The antibacterial spectra of polymyxin B and colistin are identical and there is bacterial cross-resistance to the two drugs. Colistin initially was described as being less toxic than polymyxin B, but more recently this has been disputed.[4] Reportedly, when colistin is used in doses necessary for control of systemic infections, untoward effects occur in 30 to 50% of patients.

Usually 20 to 50 mg. of colistin is given intramuscularly two to three times per day for a maximal daily dose of 150 mg., but some investigators[1] have given 300 to 350 mg/day. There is a special preparation for intravenous or intrathecal use, since the form for intramuscular use contains a local anesthetic.

When amounts of colistin are given to produce an antibacterial effect similar to that obtained with recommended doses of polymyxin B, the untoward effects of the two drugs may be similar. In addition, transient leukopenia, auditory disturbances, and hepatotoxicity may occur after colistin is used.

Cycloserine

Cycloserine (Seromycin) is active against strains of *E. coli* and *Klebsiella-Aerobacter* organisms, but *Pseudomonas* and *Proteus* organisms are often resistant. Tubercle bacilli, *Nocardia* organisms, and some streptococci and staphylococci may also be sensitive to the drug.

In infections due to gram-negative bacilli, cycloserine is used chiefly as a second-line agent in those of the urinary tract.

In normal adults the maximal oral dosage is 250 mg. every six to 12 hours, preferably the latter. To minimize untoward effects, blood concentration should not exceed 25 μg. ml. Untoward effects are likely when more than 1 gm. of cycloserine is given daily, particularly when the individual dose exceeds 250 mg.

Untoward effects of cycloserine include dermatitis, headache, drowsiness, mental confusion, hypomania, dyskinesia, and convulsions. Cycloserine's neurologic effects may be reducible by conjoint administration of pyridoxine. Cycloserine is used cautiously in patients with reduced renal function and is contraindicated in those with epilepsy.

Paromomycin

Paromomycin (Humatin) is used orally in certain cases of enteric salmonellosis, shigellosis, and amebiasis and to suppress the intestinal flora before operation as well as in patients with hepatic coma. To prevent neu-

Continued

rologic complications which may reflect the systemic absorption of ammonia due to the action of intestinal bacteria on dietary protein in patients with hepatic coma, the three drugs most commonly used are neomycin, kanamycin, and paromomycin. All three drugs have in common partial bacterial cross-resistance with streptomycin; that is, a streptomycin-resistant organism may be sensitive to the drugs, but an organism resistant to one of the drugs is also likely to be streptomycin-resistant. In addition, bacterial cross-resistance among neomycin, kanamycin, and paromomycin is usual. Paromomycin is not well absorbed after oral administration and is ineffective in systemic infections.

Paromomycin is given orally in 500-mg. doses four to six times daily; an initial dose of 4 gm. has been recommended. Excessive oral dosage is avoided since the agent is potentially nephrotoxic.

Untoward effects include dermatitis, headache, candidal superinfection, vomiting, and diarrhea. Loose stools after the drug is used may be confused with an underlying disease.

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The Mandrake

"And Reuben went in the days of wheat harvest, and found mandrakes in the field, and brought them unto his mother Leah."

From this verse and the three subsequent ones, and substantiated by Bible botany, Genesis 30:14-17 indicates that in Biblical days the mandrake plant was used for a love potion.

Besides being an aphrodisiac it was one of the many highly touted "cures," ancient and medieval. A versatile plant indeed: it was an emetic and purgative, a promoter of fecundity, a narcotic for pain. In fact, if human faith were prodigious enough, a bit of mandrake rhizome could cure anything — from abasia to zoopsia.

Similar to Mandragora and belonging to the deadly nightshade family, mandrakes were superstitiously regarded as partially human plants. Was not *man* their first syllable; did not their bifurcated roots resemble a pair of human legs; and, when forcibly extirpated, did not the plant utter a human shriek that instantly struck dead the man so bold as to disturb it?

For optimum potency mandrakes had to be quickly jerked out of the ground in a graveyard at night in the dark of the moon. Medicinal plants growing anywhere else were only moderately efficacious; but those that sprang up spontaneously in a burial ground were imbued with a special esoteric power acruing to them from the residual life force of the dead on whose graves they flourished.

In parts of Africa the mandrake is still used for its legitimate belladonna properties as a narcotic and antispasmodic.

Publicity

Publicity is easy to get. Just be so successful you don't need it, and then you'll get it. — Anon

Abstracts, Briefs and Commentaries

INKY-CAP TOXIC REACTION*

An adult woman suddenly became violently ill about one hour after having drunk a glass of sherry in the late afternoon. Her first symptom was the feeling that her head "was swelling." This was quickly followed by "shakiness," "tingling in the toes and fingers," "chills," and "gasping for breath." She also reported flushing and palpitations and stated that although her mind was clear she could not speak. She was able to talk after about one hour, at which time she was put to bed. Symptoms gradually subsided, she slept, and by morning all manifestations of the toxic reaction had disappeared. A physical examination conducted subsequently revealed no abnormalities that could be attributed to the reaction. Her husband, who had also drunk the wine, was not affected.

The important associated history is that the woman is an active amateur mycologist** and had eaten cooked inky-cap mushrooms twice a day for four days preceding the reaction. The husband also had eaten some of these mushrooms during this period, but not so frequently and in lesser quantity.

The inky-cap (Coprinus atramentarius) is a fairly common gill fungus which fruits almost any place where organic debris is present in quantity. It is most frequently seen during the spring and fall in cool wet weather and may be found in gardens, lawns, and around buildings. The popular name is derived from the fact that at maturity the gill structures blacken and liquify.

The mushroom is entirely without untoward effects unless its ingestion is associated with alcohol intake.[1] The effects are due to the presence of disulfiram in cooked C. atramentarius.[2] Other coprinius species apparently do not contain this chemical. Evidence indicates much variability in reaction to C. atramentarius when combined with alcoholic beverages. Buck[3] reports that in some cases the reaction has been observed when the mushroom was eaten during or after alcohol consumption, while in other instances no reaction resulted under these circumstances, but a reaction did occur when alcoholic beverage was consumed 24 hours later.

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*The State Department of Health would appreciate receiving other reports of this kind of toxic reaction.
**See Test Your Word Score Page 943.

Continued

The onset of symptoms, as in the present case, is abrupt and usually occurs within one to two hours of the alcohol intake. Symptoms are entirely typical of disulfiram-alcohol toxicity, and they are transitory. Factors which affect the severity of the reaction include a variability in the toxicity of the C. atramentarius itself,[1] the time relationship between the ingestion of the mushroom and the alcohol, the quantities of each consumed, and individual sensitivity to the reaction.[4]

Complete recovery may be expected within a few hours, and only conservative symptomatic management is ordinarily indicated. Unusually severe reactions may, however, warrant more aggressive therapy similar to that employed in antabuse-alcohol toxicity.

Warren K. Lawson, M.D.
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METASTATIC CARCINOMA OF THE MALE BREAST

Remission by Adrenalectomy

Adrenalectomy has been an accepted and useful method of treatment for metastatic carcinoma of the female breast. Reports concerning treatment for metastatic carcinoma of the male breast have been few. Favorable reports do indicate remission in some cases. The authors report two patients with far advanced metastases who had remissions following adrenalectomies.

Case I. In 1954 a 60-year-old Negro with broken-down primary and large metastatic axillary nodes was treated by x-ray and bilateral orchiectomy. He was not seen again for three years and then reported back with some improvement of the primary lesion; but the arm was edematous. The axillary nodes were positive for carcinoma. Again he was not seen for about two years. There was progressive swelling of the arm, and skin nodules on the chest were numerous. Examination revealed masses in both breasts, increased swelling of his arm, and frozen shoulder and elbow joints. The chest x-ray showed metastases to the lungs with pleural effusion. Bone survey revealed widespread osteolytic and osteobastic lesions. Bilateral adrenalectomy was performed. The glands weighed 23 grams and were partially replaced by metastatic cancer. He was discharged on maintenance doses of hydrocortisone and nine-alpha-fluoro hydrocortisone. Eighteen months later the ulcerative lesions were healed, the arm swelling was decreased, lung metastases were diminished, pleural effusion had not reaccumulated, and skeletal lesions showed reossification. This condition prevailed for nearly another year, after which he underwent a rapid decline.

Case 2. This 50-year-old male had a radical mastectomy for carcinoma together with bilateral orchiectomy. The patient did well for about four years, at which time he developed back pain, pleural effusion and

enlarged supraclavicular glands. The effusion was aspirated and he was put on stilbestrol. Back pain increased markedly. X-ray examination revealed metastases to the skull, the clavicle, the dorsal and lumbar vertebrae, and the sacrum. Approximately five years after his mastectomy a bilateral adrenalectomy was performed. His back pain improved promptly, and reossification of the spine was shown by x-ray. The patient returned to work about one month after his surgery. Reexamination was done, revealing excellent results.
Summary: Case 1. The 60-year-old Negro received great improvement with remission for 21 months. Case 2. The 50-year-old patient with pulmonary and osseous involvement sustained marked remission and continued to work for three years.

The authors report the follow-up on 12 patients who had adrenalectomy with remissions of from six months to five years.

Stanley R. Maxeiner, Sr., M.D.
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Joseph McLaughlin et al.: Department of Surgery, U. of Maryland School of Medicine. Ann Surg 162:#T, 1965.

PSYCHIATRIC ILLNESS IN PHYSICIAN'S WIFE

The case records of 50 physicians' wives admitted to a private psychiatric hospital were reviewed to determine what factors were relevant to their illnesses. Most of the patients became ill between the ages of 29 and 35, after the stresses of their husbands' education and early professional adjustment had been overcome. The typical patient first developed her symptoms after 12 years of marriage; the diagnoses, while varying considerably, were characterized by the primary complaint of depression, addiction to alcohol and drugs, or a functional pain syndrome.

Frequently the patient described her spouse as an inadequate father and husband, and more specifically, as undemonstrative, dependent, or domineering. More than one half felt that the frequent absence of the husband was an important factor in their illness, and many of these wives felt that their dependency strivings and sexual wishes were unfulfilled. It seemed, and especially in those suffering from drug addiction, that the patients were often given drugs (generally habit-forming ones) instead of husbandly concern and affection. As a group, these patients appeared somewhat immature and passive, although they had at one time adapted admirably. The author concluded that psychiatric illness and repeated hospitalizations for diverse reasons often indicate a faulty husband-wife relationship in which the wife is progressively excluded from her husband's life and that this neglect and exclusion is a common precipitating factor in the psychiatric illnesses of physicians' wives.

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Evans, J. L.: Psychiatric Illness in the Physician's Wife. Amer J Psychiat 122:159, 1965.

ARTERIAL DAMAGE WITH FRACTURES

Arterial insufficiency and trauma are a bad combination and if not properly attended may lead to crippling disabilities or even the loss of a limb.

Continued

The relatively deep and fixed vessels are the most commonly injured. They may be compressed, acutely angulated, torn, or, in some instances, severed. Cool, pale, dry extremities with hypesthesia, absent pulsation, decreased motor function suggest damage which should be attended as an emergency. There are few contraindications to arteriography which are valuable in identifying any significant arterial occlusion. The cases reported by Bassett and Silver indicate complete obstruction of the femoral artery from a fracture at the sacroiliac joint with compressive occlusion; a fracture about the knee from compound injury of the tibial head, and thrombosis of an internal carotid artery resulting from extensive contusions about the chin and neck.

Treatment consists of stellate ganglion block in arterial occlusion about the elbow resulting from spasm. When an artery is damaged it should be repaired by simple suture, autogenous graft, or prosthetic graft, in that order, depending upon the circumstances.

In most instances fracture fixation should be accomplished prior to arterial repair. The purpose of arterial repair is to restore the normal circulation in peripheral tissues in an effort to salvage as much of the extremity as possible.

Carl O. Rice, M.D.
Minneapolis, Minnesota

Bassett, Frank H., and Silver, Donald: Arterial Injuries Associated with Fractures. Arch Surg 92:13, 1966.

POSTSPLENECTOMY THROMBOCYTOSIS

Postsplenectomy thrombocytosis is a complication of splenectomy about which little information has been published. Two out of 3 patients suffering with this disorder and seen in the past 2 years had thromboembolic complications apparently related to their thrombocytosis; the third had hemorrhagic manifestations. Coagulation studies performed on the patients with thromboembolic difficulties revealed no abnormalities except for platelet counts which had risen from normal preoperative levels to as high as 1.37×10^6 postoperatively. Both patients had multiple pulmonary infarctions. Both symptoms and platelet levels were well controlled with small doses of uracil mustard. The patient with hemorrhagic manifestations showed abnormalities in thromboplastin generation partially corrected by normal serum, alumina absorbed plasma, and dilution of the patient's platelets. At this time, the platelet count was 2.64×10^6/cu. mm. Following therapy with uracil mustard, the platelet count fell to normal levels, the thromboplastin generation test reverted to normal, and the patient became asymptomatic. In any patient who has ever undergone splenectomy, the occurrence of hemorrhagic or thromboembolic manifestations should cause one to consider the existence of postsplenectomy thrombocytosis.

Courtesy of References and Reviews
Journal of the American Medical Association

Hayes, D., Spurr, C., Hutaff, L., and Sheets, J.: Ann Intern Med 58:259, 1963.

Derivatively Speaking

Artery — from Greek *aer* (air) + *terein* (to keep), because the ancient Greeks thought the arteries held air.

Book Reviews

Books must follow sciences, and not sciences books. — Bacon

SYMPOSIUM ON CATARACTS — **Transactions of the New Orleans Academy of Ophthalmology, St. Louis. C. V. Mosby Co., 1965. 340 pages, illustrated, chapter references, index, price $19.50.**

The material found in this book consists of the lectures and "round table" discussion of guest speakers at the New Orleans Academy of Ophthalmology Midwinter Symposium on cataracts held in New Orleans, February 16-21, 1964.

With the exception of the first chapter on the differential diagnosis of leukocoria (white pupil) in children, the special material would make interesting reading only to an ophthalmologist. The presentations are thought provoking, well illustrated, and contain numerous references. There is more than the usual number of proof-reading errors which contribute to the reader's harassment, but all in all the editors are to be congratulated for making the material available to those of us unfortunate enough not to have been in New Orleans during February 1964.

William S. McClanahan, M.D.
Minneapolis, Minnesota

FOUNDATIONS OF ANESTHESIOLOGY — **Albert Faulconer and Thomas E. Keys. Cloth. Pp. 1337. Charles C. Thomas Co., Springfield, Illinois. 1965.**

These two volumes represent a significant contribution to anesthesia literature. The compilers have assembled a representative group of "classic" writings to tell the story of the development of modern thought and practice in anesthesiology. Translation from another language was necessary to make many of the early works in this field available to the English-speaking world.

The compilers divide the study of anesthesia principles into eight subjects, including respiratory physiology, theories of narcosis and inhalation, rectal, conduction and intravenous anesthesia. The format of this book has been designed to present reports of significant ideas in their original form as they pertain to the progress of knowledge in a given field. For each of the selected subjects, these works are given in the chronological order of their appearance in the literature.

No attempt has been made to abstract, condense or interpret any of these writings. Some of the material presented has been proven to be erroneous but is included for obvious reasons of historical interest.

The appeal of such a book, as a personal possession, is limited primarily to students and instructors of anesthesiology, to research workers and to those persons who have a particular interest in the development of scientific ideas through several generations. These volumes should certainly be included in medical libraries. They fill a reference material void that has never been seriously approached heretofore.

D. Stuart Weatherhead, M.D.
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CORRECTABLE RENAL HYPERTENSION — **Chester C. Winter, M.D., F.A.C.S. Lea & Febiger, Philadelphia, 1964.**

The complexities and vagaries of hypertension caused by renal disfunction are brought into sharp focus and fine perspective by a contemporary pioneer in renal disease. The author has contributed greatly to our clinical management of hypertensive patients with introduction of radioisotope renography and methods of performing divided renal function tests. His concise and readable textbook provides basic information in all major aspects of kidney disease as it relates to hypertension. Various conflicting theories of the etiology of renal hypertension are objectively and effectively discussed and the chapters on physiology are excellently written. The author presents currently accepted techniques for correction of reduced blood flow to the kidney and summarizes results obtained by various authors. This book is of particular value for medical students, interns, and residents as they seek to familiarize themselves more completely regarding this fascinating and newly burgeoning field of medicine.

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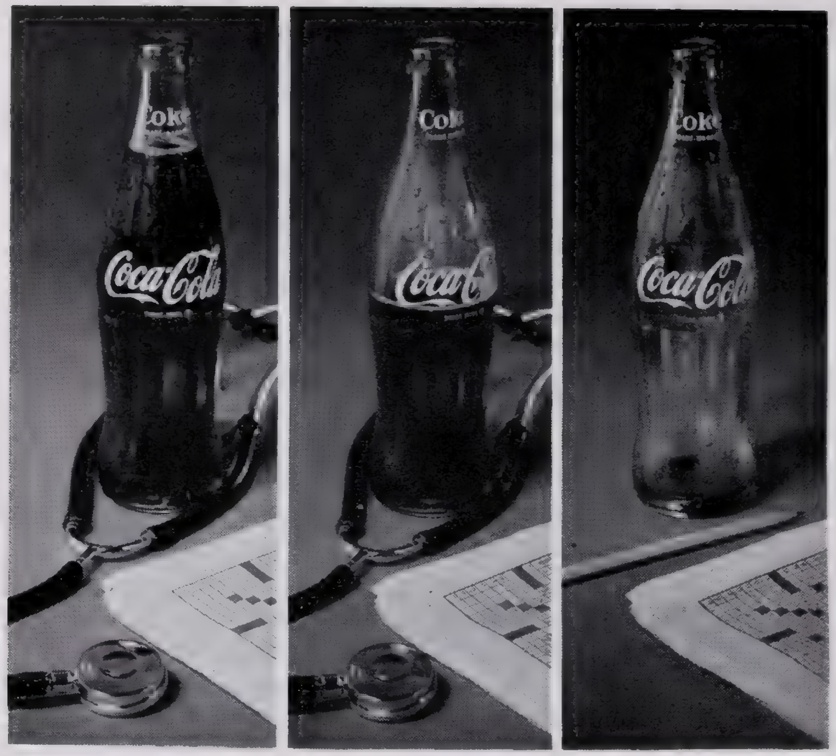

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Gleanings from the Meetings

First National Congress on Medical Ethics

Sponsored by Judicial Council
American Medical Association
March 5-6, 1966 — Chicago

The first National Congress on Medical Ethics was keynoted by James H. Berge, M.D., of Seattle, Washington. He pointed out that the purpose was to retain valuable ethics which have evolved from experiences in the past, to provide for the needs of the present, and to plan for possible changes in the future.

In most medical schools there is no course of instruction dealing with ethical considerations; but each graduating student receives from the American Medical Association a booklet outlining the principles of medical ethics to which he is expected to adhere.

Professional Ethics in a Time of Change — Everett Hughes, PhD.

Though the high principles of medical ethics can be emblazoned in the sky, the working rules which make them effective must be flexible enough to change with changing times.

Dr. Everett Hughes of Brandeis University, Waltham, Massachusetts, pointed out that the ethical errors of one individual reflect on the entire profession and, therefore, it is not the responsibility of the society to protect the errant member. The public do not doubt the judgments of their own physicians and often have more faith in them than their fellow physicians have.

Medicine — A Profession or a Business — James Z. Appel, M.D.

Dr. Appel, 120th President of the American Medical Association, speaking on Medicine as a Profession or a Business, reminds us that the inability to practice medicine may be physical, mental or professional, and that only a small percentage of physicians fall into the category of being dangerous.

Disciplinary problems that are encountered originate from the incompetent physician. Dr. Appel concurs in the recommendation of Dr. Derbyshire who has stated that, as much as possible, misconduct should be handled at the lowest level, starting with the staff. Recalcitrant members should be referred to the Grievance Committee or to the local and state society only if the problem remains unsolved. He further points out that in order to provide good public service a physician must practice self-denial, self-evaluation and self-discipline. In order to prove the true spirit of his professionalism he must render proof of his competence by being humanitarian, showing professional independence, and accepting no dictates from those not qualified to give them. He must resist interference, minimize business and financial reward, and maximize service to humanity.

Economics or Ethics — Russell B. Roth, M.D.

Dr. Roth, Chairman of the Council on Medical Service dealing with ethics and economics, pointed out that the economically and ethically sound physician causes no concern and is successful; the medically unethical physician may have difficulty within his profession; whereas the unethical

Continued

but economically-sound physician falls into the category of charleton or quack.

The physician should seek remuneration only for services performed, and his fees should be commensurate with the services rendered. Dr. Roth pointed out that the medical credit card which is being sponsored in some areas would be considered ethically out of bounds at the moment because there might be a tendency to overcommercialization. He reminded us that any form of fee-splitting is truly not in the interests of the patient.

Medical Ethics — **Robert Mayo Tenery, M.D.**

Dr. Tenery from Waxahachie, Texas, dealt with the etiquette of referrals and has suggested some rules for both the referring physician and the consultant.

Suggestions for the Referring Physician

1. Select ethical consultants of dependable ability who are courteous to your patients, charge reasonable fees, and will take your charity patients as well as your paying patients.

2. Know your consultants personally.

3. Make appointments for consultations yourself and talk with the physicians when possible.

4. Send the consultant a written summary which includes your history of the case, physical and laboratory findings, treatment and opinion of the case. Also give an indication of what you have told the patient and family, a description of any special personality traits in the patient, and a definite statement as to whether you wish merely an opinion or both opinion and treatment. Furthermore, you should tell the consultant if the patient's financial limitations may require a reduction in his usual fee.

5. Do not limit the consultant by telling the patient that a specific operation or treatment will be done; instead, tell the patient that he is being referred for an operation or treatment if the consultant agrees that it is indicated.

6. In surgical patients do not force the consultant to accept you as his first assistant. A surgeon often can do a better job when assisted by one who is familiar with his technique.

7. Give the patient an appointment for a follow-up visit. At that time you can evaluate his opinion of the consultant.

Suggestions for Consultants

1. Follow the request of the referring physician and do not take over the treatment without his permission.

2. If possible, call the referring physician immediately after you have seen the patient.

3. When another ailment is discovered, talk with the referring physician before treating this condition or referring the patient to another specialist.

4. Send a written report to the referring physician as soon as possible. This should include your findings, opinion, treatment (if any), recommendations and disposition of the case.

5. Never degrade the referring physician and be cautious in commenting on anything that he has said or done.

6. In arriving at your fee, take into consideration the patient's ability to pay the referring physician's fee plus your own.

7. Be certain that the patient returns to the referring physician when you have completed the requested service.

From the Workshop

The afternoon sessions were divided into small discussion groups in which doctors were able to express their opinions informally.

Grievance Committee — **Henry Crawford, M.D.**

From the Grievance Committee group, the consensus of opinion was that this committee should be composed of doctors only, and that it should be so handled as to provide proper public relations between disputing doctors. Most of the grievances, it was pointed out, can be handled informally and many of them by telephone. It was suggested, however, that those members who are on the Grievance Committee should check with their malpractice and liability insurance to determine whether or not they are covered against liability for slander arising out of the dissatisfaction of one who is being disciplined.

Discipline Committee — **William J. Kelly, M.D.**

From the Discipline Committee it was concluded that soft discipline by the lowest level of the local society should first be undertaken. Anyone who is being disciplined should be advised of his rights to appeal to a higher authority if he so desires. It was the consensus of the group that our obligation is to govern ourselves, but that the code of medical ethics must be satisfactorily adhered to. It was further suggested that the public be informed that we do discipline our own members.

Interpretation of Unethical Conduct by Local Standards

— John Burkhart, M.D.

Interpretation of unethical conduct on the part of an individual should be based on local standards, and it was the consensus of this committee that the problem of fee-splitting should be handled in accordance with the ethical principles set out by the American Medical Association: that a charge be commensurate with the services rendered and an assistant's fee be paid by the patient to the assistant, and that the referring physician use an assistant only if it is indicated. Overtreatment of a patient was frowned upon as being too commercial and thereby a violation of the code of ethics.

Medicine and Pharmacy Committee — Marvin Johnson, M.D., Moderator

Owning a pharmacy within the reach of one's own prescriptions would not constitute good ethics, and prescribing medications under a code name without the privilege of receiving full descriptions of the ingredients would likewise be considered poor ethics.

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Special Article

Tumor Registries in Minnesota

J. JEFFREY MCCULLOUGH, M.D.*
WILLIAM C. HARRISON, M.D., M.P.H.**
DEAN S. FLEMING, M.D., M.P.H.†
Minneapolis, Minnesota

THE STATISTICAL analysis of data pertaining to large groups of cancer patients is a valuable tool in cancer investigation. It has led to the development of many types of tumor registries where basic information and follow-up reports on each patient can be accumulated.[1-3] In 1950 there were 4,375 resident cancer deaths; 90 per cent of Minnesota hospitals reported a total of 8,445 cancer cases.[4]

There are different types of registries, each with a different goal. As described by Ringel,[5] the three basic types of tumor registries are: the very limited registry which is concerned with only one particular type of tumor (breast, thyroid, lymphoma, etc.); the epidemiological registry which involves detailed analysis of each case with attempts to make correlations of etiological significance; and the most widespread type of registry which is that found in many medium-sized hospitals. The latter type uses a limited amount of data about each case, performs some statistical studies, and serves as a basis

TABLE I
Minnesota Hospitals Which Have Cancer Registries Operating in Co-operation with the American Cancer Society and Minnesota Department of Health

Hospital	Location	Patients Registered During 1963	Total Patients Registered
1. Ancker	St. Paul	180	754
2. Bethesda	Crookston	75	298
3. Community	Cloquet	43	43
4. Glenwood Hills	Minneapolis	86	308
5. Hibbing General	Hibbing	146	907
6. Itasca Memorial	Grand Rapids	93	633
7. Lake Region	Fergus Falls	81	783
8. Lake View Memorial	Two Harbors	18	171
9. Miller Memorial	Duluth	These cases included with St. Mary's of Duluth.	
10. Mount Sinai	Minneapolis	179	1,545
11. St. Barnabas	Minneapolis	328	2,468
12. St. Francis	Crookston	39	211
13. St. Joseph's	St. Paul	192	1,411
14. St. Luke's	Duluth	373	2,556
15. St. Mary's	Duluth	311	2,265
16. St. Mary's	Minneapolis	442	2,118
17. Winona	Winona	77	363
		Average 166	Total 16,834

Continued

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*Cancer Control Officer, Public Health Service, U. S. Department of Health, Education, and Welfare, assigned to Minnesota Department of Health, Minneapolis, Minnesota.

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for "assessing the quality of care received by the patient and the effectiveness of diagnostic and therapeutic measures."[6]

Tumor Registry Hospitals

There are at present 186 hospitals[7] with 16,471 beds in Minnesota which care for acutely-ill medical and surgical patients. The 17 hospital tumor registries represent 3,731 beds or more than one fifth of the medical and surgical hospital beds for the acutely-ill in the state.* (See Table 1.)

During 1963, 126,071 patients were admitted to the 17 hospitals which comprise the basis of this report, representing an average of 7,416 annual admissions per hospital. Approximately 2.1 per cent (2,663) of these patients were entered into the tumor registries. The duration of the average hospital stay was 7.8 days with a range of 5.9 to 14.3 days.

Present Status

Survival

From 1957 through 1963, a total of 16,834 patients had been entered into the Minnesota tumor registries (Table 2). A follow-up survey was made during early 1964, which

TABLE 2
Present Status of 16,834 Patients Entered into Minnesota Cancer Registries
1957 Through 1963

	Number		Percent	
Total living	8,258		49.0	
living, with cancer		1,632		9.7
living, free of cancer		6,165		36.6
living, status unknown		461		2.7
Total dead	8,173		48.6	
dead of cancer		6,682		39.7
dead of other causes		995		5.9
dead of unknown causes		496		3.0
Lost to follow-up	403		2.4	
Total cases	16,834		100.0%	

TABLE 3
Percentage Distribution by Site of 17,301 Malignant Neoplasms in Seventeen** Hospitals 1957 Through 1963

	Ancker	Bethesda	Community, Cloquet	Glenwood Hills	Hibbing General	Itasca	Lake Region	Lake View	Mt. Sinai	St. Barnabas	St. Francis	St. Joseph's	St. Luke's	St. Mary's, Duluth	St. Mary's, Minneapolis	Winona	Average
Oral Cavity	7.4	1.0	0	2.5	4.3	2.1	3.7	2.9	4.3	1.8	2.8	6.1	1.6	3.2	3.0	3.4	3.2
Digestive	26.9	32.4	18.6	21.6	27.5	26.1	20.2	32.8	22.6	26.0	23.2	24.0	27.3	24.6	20.4	26.1	24.8
Respiratory System	8.2	6.5	4.7	6.6	7.5	6.7	4.3	2.3	8.5	6.9	3.8	11.0	7.1	10.4	12.9	5.0	8.4
Breast	10.8	12.1	23.3	15.4	7.7	11.2	22.5	14.9	11.7	15.2	12.8	15.2	12.1	13.1	13.3	21.3	13.5
Female Genital	10.4	8.2	14.0	18.8	14.8	17.8	16.6	19.0	14.4	15.2	20.4	12.3	15.4	13.7	17.4	20.3	15.1
Male Genital	12.4	12.7	11.6	7.8	3.9	6.2	6.8	4.6	5.4	4.4	10.0	7.2	12.1	8.5	7.1	6.8	7.6
Urinary Organs	5.2	2.6	0	4.7	4.3	3.5	3.7	3.4	4.7	4.2	6.6	7.5	8.1	6.9	7.6	4.2	5.8
Lymphatic and Hematopoietic	4.4	4.2	2.3	6.6	5.9	4.6	10.7	6.9	7.3	8.2	5.7	8.5	6.7	8.4	7.1	6.8	7.3
Skin	11.3	15.0	18.6	7.5	19.6	16.1	8.0	*	13.5	10.9	14.7	2.8	9.6	*	6.7	3.7	8.8
Central Nervous System	*	0	0	3.1	*	0	3.5	*	1.2	2.0	0	1.8	*	2.3	2.6	0	1.4
Other	3.0	5.3	6.9	5.4	4.5	5.7	0	13.2	6.4	5.2	0	3.6	***	8.9	1.9	2.4	4.1
Total Cases	752	306	43	319	1128	659	783	174	1545	2666	211	1411	2521	2285	2118	380	17301 (100%)

*These cases are classified as "other."
**Cases from Miller Hospital, Duluth and St. Mary's Hospital, Duluth are combined as a single registry.
***These cases are classified with "skin."

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*Federal hospitals such as Veterans Administration and the Indian Hospitals are not included in this report.

showed that 49.0 per cent of all patients were surviving at that time (36.6 per cent surviving free of cancer, 9.7 per cent surviving with cancer, and 2.7 per cent surviving with unknown status in regard to cancer).

Absence of Neoplasia

At last follow-up, more than one third of the patients (36.6%) were living free of cancer, an additional 5.9 per cent having died of causes other than cancer.

Multiple Tumors

There was a 1.4 per cent incidence of multiple primary malignancies.

Distribution by Site

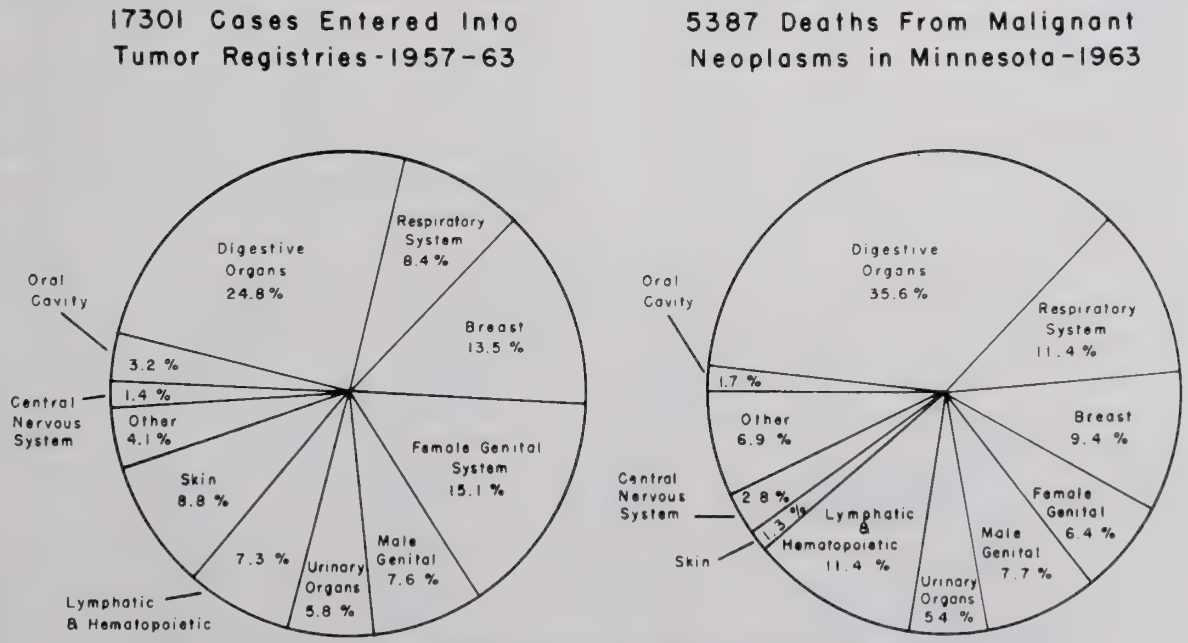
The distribution of the tumor registry cases by site in the participating hospitals is shown in Table 3. In general it appears that larger hospitals register more cancer cases, have a longer patient stay and a higher ratio of cancer cases to bed capacity, and tend to have more tumors of the oral cavity and of the respiratory, male genital, urinary, lymphatic and hematopoietic, and central nervous systems. Smaller hospitals with a shorter patient stay and a lower ratio of cancer cases to hospital beds have a higher proportion of tumors of the breast, female genital system, and skin.

In Minnesota malignancies of the breast, female genital tract, oral cavity, and skin account for a larger portion of the cancer registry cases than would be expected on the basis of deaths from these neoplasms in the state (Table 4 and Figure 1). Improved methods of diagnosis and treatment have lowered the proportion of deaths caused by some of these neoplasms and at the same time increased the number of these cases treated in hospitals which have cancer registries.

TABLE 4

Cancer Registry Cases by Site From 1957 Through 1963 Compared with Cancer Deaths in Minnesota During 1963

	Malignant Neoplasms in Cancer Registries 1957-63		Deaths From Malignant Neoplasms in Minnesota 1963	
Site	Number	Percent	Number	Percent
Oral Cavity and Pharynx	560	3.2	94	1.7
Digestive Organs	4,287	24.8	1,920	35.6
Respiratory Organs	1,459	8.4	614	11.4
Breast	2,334	13.5	508	9.4
Female Genital	2,603	15.1	344	6.4
Male Genital	1,307	7.6	416	7.7
Urinary Organs	1,011	5.8	288	5.4
Lymphatic and Hematopoietic	1,262	7.3	613	11.4
Skin	1,522	8.8	69	1.3
Central Nervous System	239	1.4	152	2.8
Other	717	4.1	369	6.9
Total	17,301	100.0	5,387	100.0


17301 Cases Entered Into Tumor Registries-1957-63

5387 Deaths From Malignant Neoplasms in Minnesota-1963

Fig. 1 — Percentage distribution of cancer registry cases and cancer deaths in Minnesota.

Continued

Functions of a Hospital Tumor Registry

A hospital tumor registry is intended to serve the hospital staff and patients as a means for improving services to cancer patients within that hospital, not merely as a repository of unused information. Ideally the tumor registry serves as the focal point of the hospital's cancer activities. It makes available to each hospital information about its own cases, not abstract survival rates compiled by a distant medical center which specializes in the care of cancer patients. At regularly scheduled tumor conferences this data should serve as a background for the discussion of the etiology, diagnosis, and treatment of malignant diseases. Several hospitals have very active tumor boards. Some have luncheon meetings at which time all new cases are presented, and pathology slides and x-rays are shown. One tumor board reviews nearly 400 cases a year; its average attendance is 30 physicians.

TABLE 6
Percentage Distribution by Site of 2,150 Malignant Neoplasms at Hennepin County General Hospital Compared with Other Minnesota Tumor Registries

	Hennepin County General	Other Minnesota Registries	All Registries Including Hennepin County
Oral Cavity	8.1	3.2	3.8
Digestive Organs	23.7	24.8	24.7
Respiratory System	6.9	8.4	8.3
Breast	8.7	13.5	13.0
Female Genital	11.6	15.1	14.7
Male Genital	8.9	7.6	7.7
Urinary Organs	5.3	5.8	5.7
Lymphatic and Hematopoietic	5.4	7.3	7.1
Skin	12.2	7.4	9.1
Central Nervous System	2.3	1.4	1.5
Other	6.9	5.5	4.4
Total Number	2,150	17,301	19,451

The tumor registry also serves to remind physicians when periodic follow-up examinations are due for particular patients. The data in these registries is more than adequate for an annual report which may include the distribution of cases by site, the per cent of diagnoses histologically proven, the trends in mortality in an individual hospital, and the completeness of follow-up care patients receive.

At some hospitals the tumor registry serves additional functions. For instance, in county institutions where large numbers of patients are attended by a continually changing house staff, problems of follow-up often arise, and patients may not receive periodic examinations for the early detection of recurrences. A tumor registry can serve as the agency for continuing contact with the cancer patients and can assist the staff in providing good follow-up care. An example of this system is presently operating in St. Paul. Many cases temporarily lost, then relocated by the cancer registry, are found to have early recurrences that would not have been diagnosed until the patient became symptomatic and sought medical attention.

TABLE 5
Present Status of 2,062 Patients in Hennepin County General Hospital Tumor Registry Compared with 16,834 Patients Entered into Remaining Minnesota Tumor Registries

	Hennepin County General		Other Minnesota Registries		All Registries Including Hennepin County	
Total living	29.0%		49.0%		45.9%	
Total living with cancer		5.6%		9.7%		9.3%
Total living free of cancer		23.4%		36.6%		35.2%
Total living status unknown		0		2.7%		2.4%
Total dead	54.3%		48.6%		49.2%	
Total dead of cancer		47.9%		39.7%		40.6%
Total dead of other causes		6.0%		5.9%		5.9%
Total dead of unknown causes		0.4%		3.0%		2.7%
Lost to follow-up	16.7%		2.4%		3.9%	
Total number of cases	2,062		16,834		18,896	

Summary

During the past 35 years there has been a gradual development of the tumor registry system in the United States to its present form involving registries with different emphases and goals. This report concerns 17 hospital registries which have been co-ordinated by the American Cancer Society and the Department of Health since 1957. More than one fifth of the acute hospital beds in the state are represented. From 1957 through 1963, 16,834 patients with 17,080 tumors were entered into the registries for an average of 2,405 patients each year. Almost one half of these are now surviving; and well over one third were free of malignant disease at last follow-up. Only 2.4 per cent were lost to follow-up during the seven-year period of this report. The digestive system was the most common site involved, accounting for almost 25 per cent of the tumors. The distribution of cases by site is presented, and a brief discussion of the functions of a cancer registry is given. Some of these registries serve the patient directly, some more indirectly. They all attempt to stimulate interest in cancer activities in the individual hospital, encourage physicians to continue patient follow-up, and thus ultimately benefit the patient.

Tumor Registries in Minnesota
Addendum

Since this article was submitted for publication, data have been received from the tumor registry at Hennepin County General Hospital, Minneapolis. Table 5 shows the condition of 2,062 cancer patients at General Hospital at the time of last follow-up and compares these figures to the averages for the other seventeen registries. The per cent of Hennepin County General patients who have died (54%) is greater than the average. However, this figure approximates that obtained from other hospitals in this group which care for large numbers of cancer patients. The largest proportion of patients who were dead at last follow-up was 63 per cent. It should be re-emphasized that these figures include patients with varying lengths of survival and thus are not comparable to standard survival rates.

The distribution by site (Table 6) for Hennepin County General Hospital is not strikingly different from the average site distribution for the other seventeen registries. There is a somewhat higher incidence of oral cancer and lower incidence of breast and female genital tumors at Hennepin County General. A similar distribution was found at Ancker Hospital.

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A Privileged Class

Most humans have doubt at sundown on many a day as to whether anything has been accomplished by them to advance the cause of mankind, or make this a better world. You've sold some groceries, written some editorials, sawed some wood, cooked some meals, written a few pages of a book or milked some cows.

Maybe you've done your best. But it's a long way from the hopper to the grist, and when the shades of evening fall the average tired soul will inescapably turn on himself with "So what?"

But a doctor who has gone into lonely and discouraged homes, where there was fear for the sick, and no one else at hand to administer remedy and give hope, can really say, "I amount to something. I'm worth while."

— Carlton K. Matson (1890-1948)

Photographic Contest

The Editors of MINNESOTA MEDICINE, in collaboration with the Doctors' Photographic Society of Minneapolis, take pleasure in announcing a monthly photographic contest. The contest is to promote an interest in photography in the medical profession. First prize each month will be publication in full color of the winning picture in MINNESOTA MEDICINE.

The following rules will govern the conduct of the contest:

1. Only doctors of medicine are eligible to submit pictures, and the picture must have been taken or composed by a physician.
2. Each contestant may submit not more than two pictures each month.
3. Only color transparencies, 35 mm. to 2¼", can be considered.
4. Each slide should be labeled with the maker's name, address, and the identifying title.
5. Slides should not be mounted on glass, but can be protected in plastic sleeves or envelopes.
6. Each entry must be accompanied by a self-addressed, stamped envelope if return of the picture is desired. Returns will be made shortly after the close of the contest each month. The winning photograph will be retained but will be returned after it has been used.
7. The deadline date for entry will be the 10th of each month and the winner of each month's contest will be announced in MINNESOTA MEDICINE in the subsequent issue. The date of publication will be three to six months in advance.
8. There will be no limitation on subject material except as indicated in item 10.
9. Model releases will be requested of winners where appropriate.
10. Judges will be selected by the editors of MINNESOTA MEDICINE and the Doctors' Photographic Society. The judges will be guided by the precepts of the Photographic Society of America, and winners will be based on appropriateness, interest, impact, and technical excellence.
11. The editors of MINNESOTA MEDICINE and the Doctors' Photographic Society cannot be responsible for entries lost or damaged, but every effort will be made to protect submitted pictures.

Your pictures are hereby invited. Please submit pictures to:

Photo Contest Editor
MINNESOTA MEDICINE

History of Medicine

The Rare Book of the Minnesota Bio-Medical Library

— a browser's view —

MARVIN SUKOV, M.D.*
Minneapolis, Minnesota

Although no one is likely to accuse Sir William Osler of idle boasting over his bibliophilic conquests, it now appears incredible that he and Dr. Harvey Cushing had shown in one exhibition six copies of the first edition of Vesalius. And while this in itself is a sufficiently enviable achievement, the great physician goes on to relate that during his lifetime he distributed copies of the Fabrica to six libraries, including the Boston Library Association and the McGill University Library. Then one day, forgetting his earlier benevolence, he offered copies of this rare book to these same libraries, only to be confronted with the invaluable gift he had previously made.

The fact that during the last generation original editions of works by medical innovators have increased in scarcity and monetary value can make us all the more grateful for the vision and zeal of Dr. Owen W. Wangensteen who made possible the Rare Book and Medical History Unit as part of the Bio-Medical Library in Diehl Hall. The story of the acquisition of funds, the search for rare volumes, the planning of the physical facilities must one day be told by himself; but rumor has it that Dr. Wangensteen was not above absenting himself from a medical meeting to pursue some elusive quarto.

While the principal interest of this collection is in the historical development of medical concepts and practice, the three thousand volumes afford the student and bibliophile a view of the development of the printing art, bookmaking, and illustration, from the mid-fifteenth century to the 1850s. It is a viable, working library with an inclusive chronological and geographic distribution. Original sources are the rule, but when otherwise not available, many items are represented by facsimiles.The Egyptologist and medical historian of preclassical cultures would seek out the original Edwin Smith Papyrus at the New York Academy of Medicine and go to Leipzig for the Papyrus Ebers. The student in Minnesota can pore over accurate reproductions of these rarities and even find a facsimile of the 1412 manuscript of John Arderne's *De Arte Phisicali et de Cirurgia,* along with others of similar nature. From the standpoint of bookmaking, the volumes range from the heavy oversize tomes of Hippocrates, Vesalius, Cowper and the Paolo Mascagni (1752-1815) anatomy with its full scale anatomical illustrations, to numerous Galenic miniatures that must have been pocketed with the devotion given a religious missal. There are ample examples of printing on parchment and fine rag paper; bindings vary from contemporary leather with brass clasps to parchment and linen; illustrations and title pages range from the elementary essential components to massively florid baroque woodblocks.

In its architectural plan this Rare Book Department is designed to serve the needs of research, teaching, and study. It has a lecture hall, class room, administrative offices, spacious exhibit hall and display cases: all with cheerful color schemes — definitely out of the fumed oak tradition — and with good lighting and air control. The book stacks, classified on the basis of life sciences under Botany, Zoology, Medicine, Dentistry, Nursing, Public Health, and Pharmacology, are housed in a well-lighted room under constant humidity and temperature. A catalogue, now in preparation, will enable the reader to select his title and have it delivered to him at the desk or to one of forty-five study carrels. Open-shelf selection, a feature of the other

Continued

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*Clinical Professor, Dept. of Psychiatry and Neurology, University of Minnesota.

I wish to thank Miss Jesse Richardson, librarian, for introducing me to the collection, and Glenn L. Brudvig, Director of the Bio-Medical Library, for the courtesy and help that he extended to me.

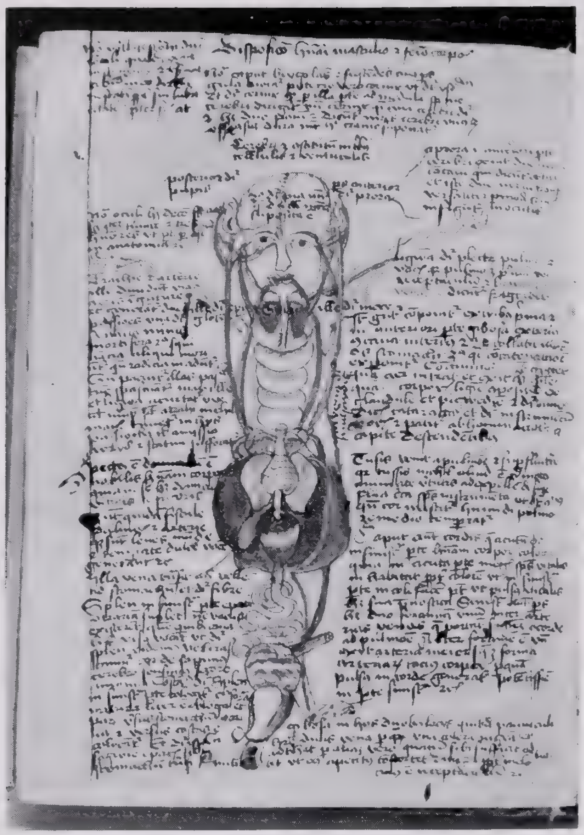


Fig. 1 — From a Medical Illustrated Manuscript of the Fifteenth Century.

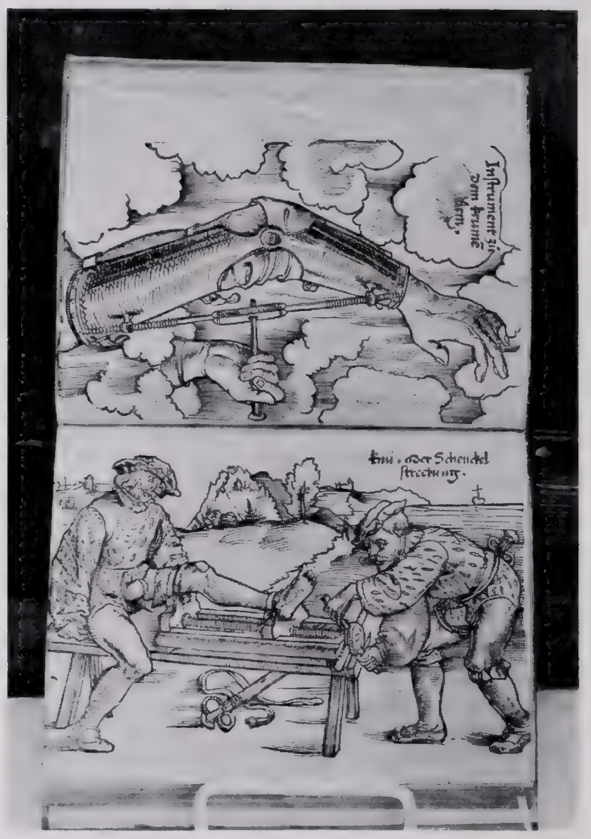

Instrument zu dem krumme Arm.
Ein . oder Schenckel streckung.

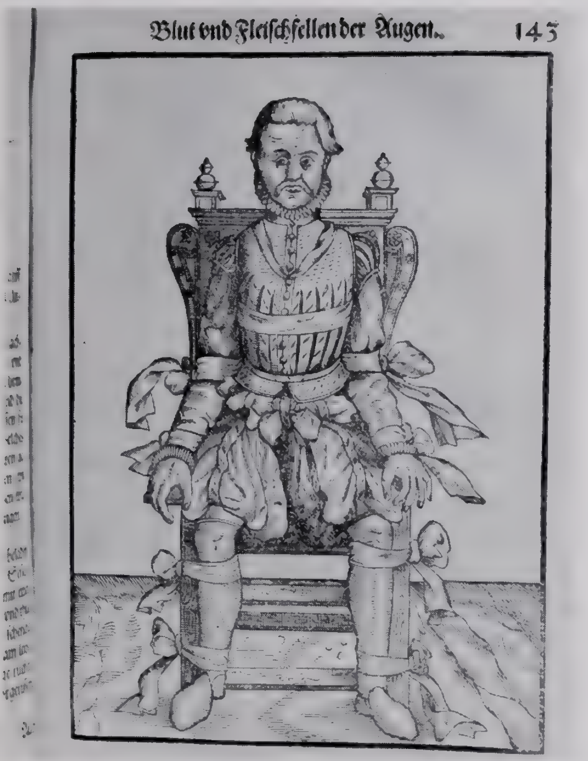
Fig. 2 — Hans von Gersdorff, *Feldtbuch der Wundtartzney*, 1526. (John Sargent Pillsbury Fund)

units in the Bio-Medical Library, is not a feasible accommodation for rare books.

One of the prize items in the library is a fifteenth-century manuscript of forty-five leaves with two colored drawings. It contains a brief text on the complexions and humors, a good diagram on urinoscopy, and an illustration based on the anatomy of some animal. The "imaginary" anatomico-physiological illustration antedates the anatomist from Brussels by a little over a century (Figure 1).

Among several incunabula is the first edition of a popular work entitled *Versehung von Leib, Seele, Ehre, und Gut* (Care of the Body, Soul, Honor, and Wealth), printed by Wagner in Nuremburg, 1489, and containing inclusive instructions all the way from nursing the sick to making a will. It is a fine copy, in its original leather with brass corners and locking hinge, printed in German Gothic with block floral initials. The flyleaf, an illustrated water color, shows a pallid patient in bed, and standing by him are a nurse, a physician, and a priest, with a professional mourner seated at the foot of the bed, awaiting the outcome. Another incunabulum is a thin 80-page volume of Mondino de Luzzi, who taught at the University of Bologna and published a manual of human dissection in 1316. Although Mondino dissected an executed criminal and is credited with reintroducing human dissection, he followed the continental Galenic description of the various organs and, curiously, the only woodcut in this volume shows a "professor" on a high-backed chair directing his "student" in the dissection. Anatomical illustration had not yet made its entry.

Hans von Gersdorff (fl. 1490-1520) practiced as a military surgeon for forty years, and while he opposed Pare's innovations, he was generally more conservative than his predecessors in wound treatment and inclined to the use of warm, not boiling, oil, as a dressing, as well as to the covering of an



Blut vnd Fleiſchfellen der Augen. 143

Fig. 3 — Georg Bartisch, *Ophthalmodouleia*, 1583.

amputation stump with a flap of skin and muscle. He is here represented by the rare second edition of *Feldtbuch der Wundartzney* (Strassburg, 1526), parchment bound. The volume has several woodcuts depicting such things as an instrument for removing depressed skull fractures, the application of variously shaped cauteries, instruments for reducing fractures of the extremities (Figure 2) and the first known illustration of an amputation. A companion volume to von Gersdorff is Hieronymus Brunschwig's *The Noble Experyence of the Vertuous Handywarke of Surgeri*, London, 1525. First published in 1497, it has priority as the first detailed account of the treatment of gunshot wounds. Peter Uffenbach's (d. 1635) huge, single-volume, surgical anthology of 1164 pages plus a detailed index, published in Franckfort in 1610, is also available, printed in small Roman type and parchment bound. The greying rag paper is still vital and pliable. Another noteworthy volume is the *Thesaurus Chirurgiae*, copiously illustrated with black and white woodcuts and closing with a flamboyant colophon — a richly-ornamented square woodcut of a wreathed male figure riding a winged stag and wielding a serpent in his left hand and a serrated sickle in his right.

The Vesalius is a fine second edition copy (1555) and is essentially identical with the first edition, except that a few changes have been introduced in the cardiovascular system. All the drawings were made by John Stephen of Calcar, a pupil of Titian, and were transported across the Alps to Basel for the press of Johannes Oporinus (1507-1568), the printer of Luther's writings. The fine lettering and good presswork, along with the superb illustrations, have made this a typographical as well as a medical classic.

Within a year of the publication of the Fabrica, Johannes Froben (1460-1527), printer for Erasmus and publisher of several works of the church fathers, issued the first Greek Galen. The volume in the Minnesota collection has over 1500 double-column pages in heavy Roman type. It may be noted that England, in spite of the efforts of Linacre and others, was slow to turn from Latin to the original Greek for the writings of Galen. Nonetheless, from the beginning of printing to the end of the sixteenth century, or during a period of about one hundred and fifty years, over a hundred publishers were putting out Galen's works in France, a somewhat larger number in Italy, and seven in England. There are some forty copies of Galen in the Minnesota collection, attesting to his popularity, which continued into the nineteenth century.

The worm-eaten condition of the extremely rare first edition of *Ophthalmodouleia* of Georg Bartisch (1536-1607) adds to its interest. Bartisch gives preoperative procedures for both the patient and the operator: the former to abstain from food and the latter from drink and venery. Considered the founder of modern ophthalmology, his book is well illustrated with superimposed anatomical plates and is presumed to contain the first detailed procedure on excision of the eye in man (Figure 3).

The seventeenth century has fulsome representation from Thomas Willis (1621-1675) and Thomas Sydenham (1624-1689).

Continued

Latin was still the rule until the end of the seventeenth century, and both of these English pioneers have their work available in the original as well as in translation. Sir Christopher Wren illustrated Willis' *Cerebri Anatome* of 1664 (found in the Minnesota collection in a later edition of his *Opera Omnia*).

Going into the eighteenth century one encounters Herman Boerhaave (1668-1738) on diseases of the eye, Nicholas Andry de Bois-Regard on orthopedics in an English edition of 1743, and an early volume of Thomas Bartholin (1616-1680), the last a presentation copy to Dr. Wangensteen on the occasion of his Samuel C. Harvey lecture at Yale. As one gets further into the eighteenth and early nineteenth centuries, the library holdings grow too numerous to list even the more important items.

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Gulliver's Travels — Jonathan Swift*

Gulliver, who had been employed as a surgeon on the sailing vessel, Adventure, encountered illness among his sailors and because of their dissatisfaction with his services they cast him onto an island ruled by a herd of Victorian horses. He learned to speak their language and found them to be a very noble species which knew no evil and lived by the infallible laws of nature. A species of monkey-men called Yahoos, having the physical characteristics of humans and, in addition, possessing all of the evil characteristics inherent in man, were held in subjugation by the noble horses.

In one of their conversations the master horse desired to know from Gulliver the reason for such unaccountable evils as he had catalogued in describing the people of his homeland.

Gulliver — On the Dissipations of Humans

"I told him we fed on a thousand things which operated contrary to each other; that we ate when we were not hungry, and drank without the provocation of thirst: that we sat whole nights drinking strong liquor without eating a bite: which disposed us to sloth, inflamed our bodies, and precipitated on prevented digestion. That prostitute female Yahoos acquired a certain malady, which bred rottenness in the bones of those who fell into their embraces: that this and many other diseases were propagated from father to son; so that great numbers came into the world with complicated maladies upon them.

That besides real diseases, we are subject to many that are only imaginary, for which the physicians have invented imaginary cures; these have their several names, and so have the drugs that are proper for them; and with these our female Yahoos are always infested."

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*See Minnesota Med 49:850, 1966.

Medicine and Religion

The Difference Between Psychiatry and Religion*

IN HELPING people in distress, there is no argument that psychiatry and religion should not cooperate; but the two fields are different. The professionals involved have different roles, use different languages and symbols, and are under different auspices with different functions. Boundaries should be defined, so that each can understand and evaluate the efforts of the other.

The main function of psychiatry is diagnosing and then making a disposition. The basic function of religion is worshipping God and advocating a moral life — not relieving anxiety or solving problems. In order for a psychiatrist to function and utilize psychotherapy, he must have a diagnosis. Clergymen on the other hand, do not need a diagnosis; all that is essential is the call or need for help.

Psychotherapy is an integral part of the practice of medicine and is a controlled scientific technique with different therapies for different categories of mental illness; to be practiced effectively psychotherapy requires a broad background of medical knowledge, special skills, and much experience after training. This does not mean, however, that the clergy do not have at their disposal other methods more comparable to first aid and including management, advice giving, teaching, and counselling. In fact, clergymen are important front-line mental-health workers, since the largest percentage of patients with emotional illness consult their clergymen first — actually 42%. Twenty-nine per cent consult their family doctors; 18% consult psychiatrists and psychologists, and 10% consult social agencies or marriage clinics. In this same study,[1] follow-up of those seen first by the clergy reveals that one of three was eventually found to be severely ill psychiatrically, and yet only one of ten had been referred by the clergy for psychiatric help. This indicates that clergymen need more training in order to proceed more effectively in the mental-health field.

Since clergymen are in the so-called "front line" and people who are "hurting" consult them first, it is important that psychiatrists, as well as physicians in general, should recognize the distinct qualifications of the clergy in special areas. Clergymen are most valuable when a religious person is suffering the severe consequences of real guilt; it is then that psychiatrists should refer that stricken person for forgiveness and guidance and should not institute psychotherapy. On the other hand, if distress results from guilt that has no basis in reality, the patient should be in the hands of a psychiatrist and so referred by the clergy. The clergy should limit themselves to reality problems.

In dealing with "front line" emotional emergencies and in counselling, the clergyman has some unique aspects which psychiatrists do not have.

1. He is considered a friend by the disturbed person and family and can even come in to help without being called directly.

2. He is around at times of stress, which include weddings, funerals, baptisms, etc.

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*Presented at the Symposium on Medicine and Religion presented at the meeting of the Hennepin County Medical Society on March 7, 1966.

Continued

3. He can give advice, castigate, rebuke, inspire, encourage, console at appropriate times. This function can and should include helping his congregation to accept psychiatry as an integral branch of medicine.

4. He stands in place of God, can use prayer, give absolution, and help to save souls.

5. He can give money, food, shelter.

In the above capacity, each clergyman is committed to his moral and religious code and preaches it publicly to his congregation; while the psychiatrist's ethical and religious beliefs are private, and he is not the custodian of his patient's morals as is the clergyman. The psychiatrist has only one role to play for each particular patient, namely, that of psychotherapist and physician, while the clergyman has many roles to play.

Irving C. Bernstein, M.D.
Minneapolis, Minnesota

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*Associate Clinical Professor Psychiatry, and Obstetrics & Gynecology, University of Minnesota.

Reference

1. Joint Commission on Mental Illness and Health — Action for Mental Health. Basic Books, Inc. New York, 1961.

The Minnesota State Board of Medical Examiners

Notice is hereby given, pursuant to the provisions of Minnesota Statutes, 1965, Section 15.0412, that the Minnesota State Board of Medical Examiners will hold a public hearing on Saturday, July 16, 1966, at 10:00 o'clock a.m. in the Colonial Room of the Lowry Hotel, Saint Paul, Minnesota, on the adoption of the following proposed changes in the Rules and Regulations of the Minnesota State Board of Medical Examiners:

1. The adoption of a new Rule and Regulation ME 7 (a) (8) reading as follows:

"(8) On all applications filed on or after July 1, 1968, evidence satisfactory to the Board that the applicant has been awarded a Standard Certificate by the Educational Council for Foreign Medical Graduates, certifying to the applicant's formal education, his having passed the ECFMG English test, and his having passed the American Medical Qualification Examination of the ECFMG."

The effect is that from and after July 1, 1968, graduates of foreign medical schools who apply for admission to a licensing examination must furnish evidence satisfactory to Minnesota State Board of Medical Examiners that the applicant has been awarded a Standard Certificate of The Educational Council for Foreign Medical Graduates, in addition to the other information required by ME 7 (a).

2. The amendment of Rule and Regulation ME 6 by striking and deleting therefrom ME 6 (b) (6) and by substituting in lieu and in place thereof:

"(6) Evidence satisfactory to the Board that the applicant has been awarded a Standard Certificate by The Educational Council for Foreign Medical Graduates, certifying to the applicant's formal education, his having passed the ECFMG English Test, and his having passed the American Medical Qualification Examination of the ECFMG."

The effect is to conform to present practice by eliminating the requirement by applicants for a temporary certificate for graduate training, that they be registered by Minnesota State Board of Examiners in the Basic Sciences, and by substituting the requirement that they have been awarded a Standard Certificate of The Educational Council for Foreign Medical Graduates, in addition to the other information required by ME 6 (b).

J. P. Medelman, M.D.
Secretary-Treasurer

HEARING · SEEING · LEARNING

Special Report

Pre-School Survey Saves Vision and Hearing

A PUBLIC HEALTH nurse advises that a child who has long been a behavior problem be given an eye examination because his eyes appear to be slightly crossed. Correction of the eye defect results in improved behavior. A child in a school for the mentally retarded is found to have a severe hearing loss. Further testing indicates that his IQ has been grossly underrated.

A child's loss of sight or hearing are subtle defects. Too often they go unnoticed because there are no manifest symptoms, or the parents of the child may not be knowledgeable about eye and ear health and do not recognize the danger signals. The only effective way of detecting these children on more than a piecemeal basis is through screening.

Obviously, the medical profession is not numerically strong enough to conduct the kind of screening which would be necessary to detect the children who are victims of eye and ear defects. While school and public health nurses often do routine screening, the children screened are generally at an age when even if discovered, many defects can no longer be corrected.

The lack of an adequate mechanism for the detection of vision and hearing defects in pre-school children prompted the establishment of the Pre-School Medical Survey of Vision and Hearing, a public service organization sponsored by the Minnesota State Medical Association. The Survey is unique in that screening of the pre-school children is done by medically-trained, but non-professional, volunteers. Various volunteer organizations have cooperated with the Survey in providing screening in their communities. Men's organizations often sponsor the program financially while the woman's groups do the actual screening. The Women's Auxiliary of the Minnesota State Medical Association has proved to be particularly effective in promoting the Survey throughout the state.

The screeners for the Survey are trained by volunteer demonstrators through the use of medically edited films, demonstration of the techniques used, and by practice sessions with kindergarten children. At present there are nineteen women who have qualified to train volunteer screeners for the Survey through a training course at the University Hospitals, as well as firsthand experience in screening.

The emphasis of the Survey is entirely medical. No volunteer organization is allowed to conduct a screening unless it agrees to abide by the medical directives of the Board of Directors of the Survey. Endorsement of the Survey is sought from the county medical society, and all physicians in the community are informed of the purpose of the Survey. If a child has a suspected hearing or vision defect, he is referred to his family physician or a medical specialist. (The screeners, however, do not recommend any particular doctor.)

The Pre-School Survey is a multi-purpose organization. One of its prime objectives is to promote parent and community education in vision and hearing health. In each community in which the Survey is conducted, an intense effort is made to reach the families of four-years-olds with information about the importance of screening and a request for

Continued

cooperation. Leaflets have been prepared for distribution to the parents at the time of screening. These are written in carefully worded, non-technical language and explain the importance of good ear and eye health.

Special leaflets which explain the nature of the child's defect are given to the parents of those children who are referred to a physician for examination. The volunteer screeners do not answer medical questions from their own knowledge. They are instructed to have the parents consult their family physician if the answers to their questions cannot be found in the literature. Local newspapers are widely used to inform the community of the nature and purpose of the Survey.

How does the volunteer screener test the four-year-old child? At this age, the child's senses are not fully developed. He has not had the educational or social training for understanding and cooperating with the screening techniques. His attention span is short. Through experience, the Survey has developed special techniques for working with such young children.

The screening tests are introduced to the children as games. Local sponsors of the Survey are urged to publish a picture of the Snellen E, which is used to test visual acuity, in their newspapers. In advance publicity, parents are asked to teach their children the "E game" in which the child indicates the position of the E with a hand or finger. The ushers at the screening center also teach the waiting children a game using the picture board from the hearing screening device so that they will be familiar with this screening technique.

Besides testing visual acuity, the screeners also check for muscle imbalance using a flashlight and an occluder. Any child whose eyes exhibit a constant deviation or a suspected tendency to deviate is referred for examination. Criteria for referral of children for medical examination have been carefully determined. Any child who is unable to read half of the 20/40 symbols with either eye or who has a visual discrepancy between the right and left eye of more than one chart line is referred for examination. The screeners are also instructed to refer children with any other signs which may indicate eye trouble, such as red or crusted lids or eyeballs.

Because the volunteer screener would be

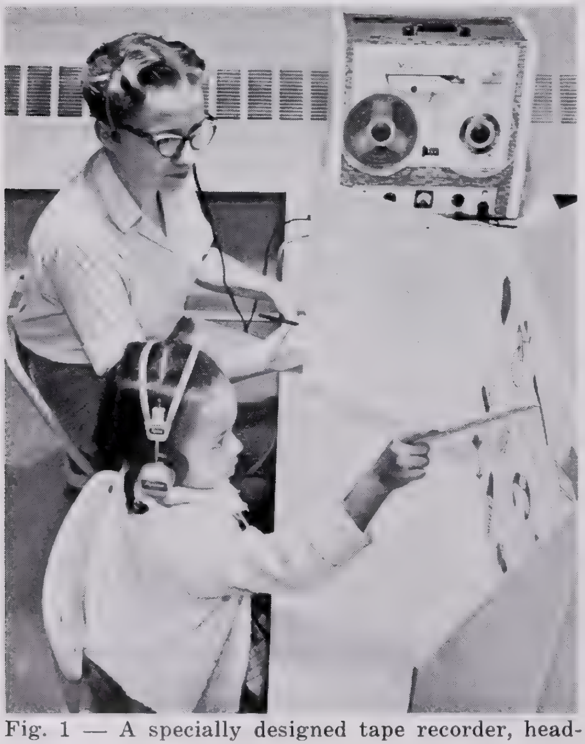


Fig. 1 — A specially designed tape recorder, headphones, and the picture screen comprise the equipment for the Visual Auditory Screen for Children.

Fig. 2 — There was no apparent evidence that this child used only one eye.

unable to conduct a reliable test with the puretone audiometer and the efficacy of a questionnaire answered by the parents is doubtful, special equipment is necessary for use in hearing screening of pre-school children. A group of audiologists under the direction of Dr. K. M. Simonton has developed a screening device called the Visual Auditory Screen for Children, or VASC.

Testing two children simultaneously, the screeners do not attempt to make a precise measurement of hearing with the VASC machine. In most cases, however, the machine will detect a hearing loss within a range from slight to severe.

The child being tested is seated before the test board on which pictures of familiar objects are mounted at random (See Figure 1). Through the earphones, he hears a series of twelve words with each ear and is asked to point to the picture of the object mentioned. Each ear is tested separately, and the screener, seated behind the child, is able to hear the tape and score the child as he takes the test. The intensity of the tape is decreased in predetermined steps from a level of 51 decibels to 15 decibels. The child's ability to hear the tape closely approximates his ability to hear normal conversation, and any child who successively misses several words or who misses two of the last three words at the 15 Db. level fails the test and is referred. When a child is referred for examination, the parent is given a referral card addressed to the physician with the option to return for rescreening if desired.

A perusal of Table 1. indicates the growth of the Survey during its five-year history. Beginning with screening in two communities in 1961, the Survey covered sixty-one towns in 1963. This year seventy-two surveys are already planned.

The table also indicates one of the major difficulties encountered by the Survey — the follow-up on children referred for examination. Approximately 50% of the medical reports have been returned to the Survey Headquarters. It is known that more action is taken on referrals, but medical reports are in many cases mislaid or forgotten. Thus figures on positive reports are conservative. Because these statistics do not give an accurate picture of the work of the Survey, the Board of Directors has decided that, beginning in 1966, records will be kept of all known action taken on referrals whether or not a signed medical report is received.

The physician in the community in which there is a survey can be of great assistance. He is in a position to encourage his patients to cooperate with the Survey and to follow the recommendations of the screeners. Occasionally there is a false positive report. It is important for the physician to be able to interpret the necessity of the survey even in cases of a false positive report. The value in identifying a potentially crippling defect in one child far outweighs the inconvenience to the parent of a child who has been mistakenly referred.

A 16 mm. informational film is available for loan from the Survey Headquarters. This

TABLE I
Report of the Pre-School Medical Survey of Vision and Hearing

	1961	1962	1963	1964	1965*	5-Year Total*
Children Screened	1546	5352	6071	6772	9151	28,892
Children Referred						
Vision	96	199	275	337	543	1,450
Hearing	151	433	577	655	1002	2,818
Total	247	632	852	922	1545	4,268
Medical Reports					Incomplete	Incomplete
Vision	44	104	160	210	250	768
Hearing	76	251	312	358	518	1,515
Total	120	355	472	568	768	2,283
Medical Reports — Positive					Incomplete	Incomplete
Vision	40	83	104	141	153	521
Hearing	58	210	255	281	410	1,214
Total	98	293	359	422	563	1,735

*Medical reports from fall, 1965, will be coming in throughout the next six months. The figures given for 1965 and the five-year total are accurate as of March 8, 1966.

Continued

is an excellent introduction to the Survey for both the medical profession and volunteer organizations which may wish to sponsor screening.

The value of the Survey is quite evident. The files of the Pre-School Medical Survey of Vision and Hearing are filled with case histories of children who have been helped as a result of early detection through screening.

Case Reports

Case 1

Routine vision screening carried on by medically-trained volunteers in the spring of 1965 in a PTA-sponsored survey in cooperation with the Pre-School Medical Survey, revealed that this child, who appeared entirely normal, relied entirely on one eye (See Figure 2). Medical examination showed a tiny cataract had caused him to avoid use of the eye and vision simply did not develop. Surgery was considered, but not advised at that time. However, the immediate need was to force the development of vision by use, inspite of the obstruction. Thus the better eye was patched. Results have not yet been assessed, but the potential for useful vision will remain, having been fostered at the only age (before six) when this could be done.

Case 2

A five-year-old boy seemed to the kindergarten teacher to be "slow," and she asked the counselor to test him. He was assigned tentatively an IQ of 51. He repeated kindergarten. His speech improved little, but he went into the first grade on trial. The school nurse giving a routine eye test, thought she detected signs that he did not hear when he could not see her face. Her test with the puretone audiometer seemed implausible. She repeated it several times and finally reported a suspected hearing loss to the parents. The otolaryngologist found a loss of around 70% in one ear and 28% in the other. The child was a candidate for a hearing aid, but this was refused unless the child's educational program was revised more in line with his needs. The audiologist stressed that the mental retardation assumption was just plain wrong. He pointed out that the boy had used self-taught lip-reading to "get by" three separate teachers, none of whom suspected his hearing loss. The school agreed to give speech teaching by a specialist, academic coaching, and to hire a special tester to make the estimation of academic potential again with tests appropriate to individuals with hearing loss. The child received a hearing aid. At last report, he was forging ahead, but there was much lost ground to make up academically and with respect to speech. The best news was the improvement in his emotional adjustment to school. Had this child's hearing loss been detected by screening at age four, it is quite probable that his IQ, now determined in the neighborhood of 100, would never have been so underestimated, he need not have repeated kindergarten, and the damage to his morale would have been greatly lessened. Chances are that his speech problems would have been much less severe.

From cases documented by the Survey, one can see that in many instances even the conscientious parent or teacher does not notice that Johnny or Jane does not see or hear well. Symptomatic behavior may be attributed to some other cause, or to a certain extent, the child may have accommodated himself to his limitations. The Pre-School Medical Survey of Vision and Hearing has provided the medical profession with a valuable tool for preventing crippling loss of sight and hearing among the children of Minnesota. With the cooperation of volunteer screeners, parents, and the medical profession, the Survey will become increasingly more effective in serving the people of the State.

Acknowledgment

When it comes time to express appreciation for a wonderful job done, particularly when many many volunteers have given so much of their time and effort, it is usually very difficult to single out any one individual for outstanding service. However, Mrs. John B. Stoltze, who has so capably served as Executive Secretary to the Pre-School Medical Survey of Vision and Hearing since its inception in 1961, richly deserves the credit for spark-plugging this organization from its infancy to its present growth. She has worked untiringly, sometimes against great odds and discouragement, and she has succeeded not only in organizing the work itself, but in rendering a real service to the younger generation in Minnesota. The members of the Minnesota State Medical Association wish to express their sincere appreciation to Mrs. Stoltze for a job very well done.

References

1. Griffing, Terry S., Simonton, Kinsey M., and Hedgecock, LeRoy D.: Verbal Auditory Screening for Children. Minnesota Med 45:35, 1962.
2. Hartman, Evelyn E.: Screening Preschool Children for Hearing Loss. Minnesota Med 48:527, 1965.
3. Unpublished material from the Pre-School Medical Survey of Vision and Hearing.

Wisdom whispers, stupidity shouts.

Meetings and Announcements

In proportion as our own mind is enlarged we discover a greater number of men of originality. — Commonplace people see no difference between one man and another. — Pascal

JUNE

Twenty-Third Annual Meeting American Geriatrics Society, Palmer House in Chicago, June 23-24. No registration fee: Contact: Edward Henderson, M.D., 10 Columbus Circle, New York.

Minnesota Academy of Medicine President's Meeting, June 8, Town and Country Club, St. Paul at 6:30 p.m.

St. Louis County Medical Society Executive Committee Meeting, 6:00 p.m., St. Luke's Hospital in Duluth, regular meeting, 8:00 p.m.

115th AMA Annual Convention, Chicago, June 26-30. Contact: AMA in Chicago for reservations.

American Proctologic Society, Statler Hilton, Boston, June 15-18. Administration Secretary: Harriette Gibson, 320 W. Lafayette, Detroit.

Idaho State Medical Association (E), The Lodge, Sun Valley, June 25-28, Exec. Sec. Armand L. Bird, 358 Sonna Bldg., Boise.

Society of Surgery of the Alimentary Tract, Barbizon Plaza, New York, June. Exec. Sec.: John Van Prohaska, M.D., 950 E. 59th St., Chicago.

Eighth Annual AMA-ASHA Preconvention Session on School Health, 7:30, Sunday, June 26, Palmer House, Chicago. Write: Department of Health Education, AMA, Chicago.

Rehabilitation Nursing Courses, June 6 through June 24, 1800 Chicago Avenue, Minneapolis. Contact: Jean R. Plass, R.N. at the American Rehabilitation Foundation.

JULY

Rocky Mountain Cancer Conference, July 15-16, at Brown Palace Hotel, Denver, Colorado. Contact: Rocky Mountain Cancer Conference, 1809 East 18th Avenue, Denver, Colorado.

American Veterinary Medical Association, Minneapolis, July 13-18. Exec. Sec.: H. E. Kingman, Jr., DVM, 600 S. Michigan, Chicago.

University of Colorado School of Medicine postgraduate courses: July 11-14, Estes Park on Ophthalmology; July 17-23 for 12th Annual General Practice Review and July 27-29, Aspen on Dermatology. For further information: University of Colorado, 4200 East Ninth Avenue, Denver, Colorado.

Symposium on Applications of Physics to Medicine, (Sponsored by the American Association of Physicists in Medicine and the University of Wisconsin Medical Center), University of Wisconsin, Madison, June 9-11. Info.: J. R. Cameron, Dept. of Radiology, University of Wisconsin, Madison 53706.

Symposium on Clinical Aspects of Renal Disease — Ischemic Heart Disease and Cardiac Diagnosis (Sponsored by Tidewater Heart Association, Council on Clinical Cardiology, American Heart Association), Cavalier Hotel, Virginia Beach, Va., June 30-July 2. Info.: Bernard H. Miller, M.D., Tidewater Heart Association, 702 Duke St., Norfolk, Va. 23510.

ANNOUNCEMENTS

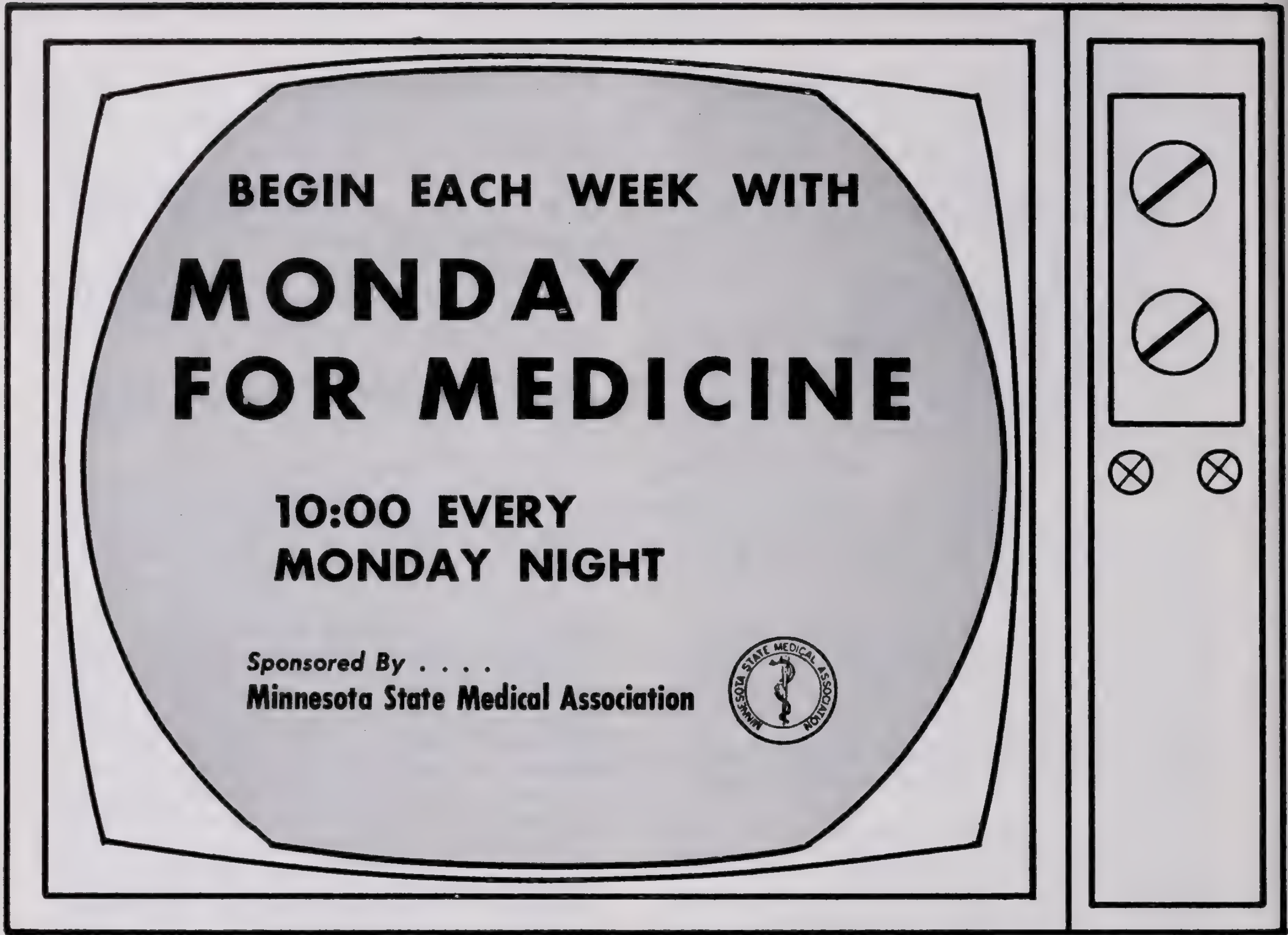
Minnesota Surgical Society Annual Essay Prize to be awarded in November, 1966. Prize of $500 will be given for the best paper on a surgical subject submitted by a medical student, intern or resident. Papers directed to surgical research and papers on clinical topics are acceptable. Deadline for submission of manuscripts is August 1, 1966. Send papers to: John F. Perry, Jr., M.D., St. Paul-Ramsey Hospital, 640 Jackson St., St. Paul.

* * *

Medical Missionary Program

The American Medical Association's 115th Annual Convention in Chicago June 26-30, will feature a series of programs, over a four-day period. The AMA Department of Medicine and Religion is focusing attention on the programs in recognition of the recent increased involvement of American physicians in world-wide humanitarian work. Special Sessions: The programs will be of interest to the physician who donates his time and skill to medical missionary work on a short-time basis, as well as those who devote extended periods of time or their careers to such work.

Southeast Asia: On Monday, June 27, the medical missionaries will be able to attend the meeting of the AMA's Section on Military Medicine. On Wednesday, June 29, a special reception will be held for medical missionaries and those interested in the medical missionary field.



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Channel 10 APPLET

Physician's Diary

False friends are like our shadow, keeping close to us while we walk in the sunshine, but leaving us the instant we cross into the shade. — Bovee

Dr. D. W. Feigal, Wayzata, has been elected president of the Hennepin County Academy of General Practitioners, and **Dr. M. B. Divertie** of the Mayo Clinic is the new president-elect of the Rochester Rotary Club.

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Dr. F. N. Grose was recently honored for ten years of service at St. John's Hospital at Browerville. An open house was given to celebrate the occasion.

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Dr. and Mrs. V. M. Johnson of Dawson were honored recently by the residents of that community on occasion of their 25th wedding anniversary.

* * *

Dr. Murray H. Hunter of Farmington has been elected to active membership in the Academy of General Practice, and **Dr. George O. Hilgermann** of Wayzata has been elected to a fellowship in the American College of Surgeons.

* * *

NEW LOCATIONS . . . **Dr. John R. Fisher** will leave Blooming Prairie for additional training at the Washington University School of Medicine in St. Louis, Missouri . . . **Dr. Charles I. Benjamin** will be associated with **Dr. Gordon E. Lee** in the Lee Clinic in Glenwood . . . **Dr. Orville P. Swenson** of Carlton has left for active duty with the armed forces . . . **Dr. Lawrence Boies, Jr.** is practicing medicine in the Wayzata Medical Building . . . **Dr. Victor M. Colago** will start practicing medicine at the Browns Valley Community Clinic . . . **Dr. Leo Grieben** joined the Hastings State Hospital staff in January.

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Dr. Norman W. Hoover and **Dr. Thomas P. Comer** of Rochester, **Dr. Matthew J. Wier** of Virginia and **Dr. Perry H. Engstrom** of Wheaton have volunteered for Project Viet-Nam. Doctors will work in provincial hospitals in various sections of Viet-Nam, where they will minister to sick and wounded Vietnamese civilians.

* * *

Dr. E. E. Zemke of Fairmont has been elected chief-of-staff of the Fairmont Community Hospital, and **Dr. Robert Zemke** will serve as secretary-treasurer. **Dr. William Feigal** has been named vice president.

* * *

Dr. Owings W. Kincaid of Rochester has been elected a fellow of the American College of Radiology.

* * *

Dr. James Janecek, an asistant professor of psychiatry at the University of Minnesota hospitals, has joined the St. Paul-Ramsey hospital staff in psychiatry. He will be director of the in-patient service.

* * *

Dr. Victor Johnson, director of the Mayo Graduate School of Medicine for the past 18 years, and **Dr. Gershom J. Thompson**, noted Mayo Clinic urologist and cancer specialist, are retiring from the Mayo Clinic. **Dr. and Mrs. Johnson** plan to move to the Island of Majorca in the Mediterranean; however, **Dr. Thompson** has no definite plans for the immediate future.

* * *

Five new staff physicians joined the Mayo Clinic in April. They are: **Doctors Ronald F. Kettering, Robert V. Groover, Colum A. Gorman, Paul Didisheim** and **Richard A. De Remee.**

* * *

Dr. C. A. Anderson of Hector recently attended a post-graduate course in medicine at Fort Lauderdale, Florida.

* * *

Dr. David Halvorson of Northfield is the newly elected president of the Rice County Medical Society. Other officers are: **Dr. Richard Meyer** of Faribault, vice-president, and **Dr. Richard Searl** of Faribault, secretary.

* * *

Dr. Harry J. Smith of Lake Crystal was recently elected head of general practice of the Immanuel Hospital in Mankato. **Dr. B. N. Batdorf** of Mankato is the new president, and **Dr. D. E. Flentje** of Mankato is the new vice-president.

This "case history" runs to some 10,000 pages

This is a typical "case history" of one new drug – or, rather, a proposed new drug – assembled for submission to the U.S. Federal Food and Drug Administration. These volumes are the result of several years' work by thousands of professional and skilled personnel in just one pharmaceutical company's research laboratories, and by hundreds of physicians in medical schools, hospitals, and private practice. They cover every aspect of experience with this proposed new agent from chemical laboratory to clinic, from mouse to man. Each volume could conceivably represent hundreds of thousands of dollars of financial investment, countless hours of human effort. This veritable mountain of data stands behind every new agent offered to you by pharmaceutical manufacturers – a reassuring testimonial to the efficacy, safety and purity of the drugs you will prescribe today to lower the cost of disease to your patients.

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This message is brought to you as a courtesy of this publication on behalf of the producers of prescription drugs.

Medical Economics

Partnership Retirement

Without a separate and specific investment plan funding the retirement program, it is not economically sound. We do not think that retirement of a partner should ever be funded out of current and future income of the remaining partners. Beyond a retiring doctor's equity in physical assets and partnership accounts, any payments to him for retirement should be funded by some investment program and based upon that doctor's specific equity or contributions to the fund.

In our opinion, any attempt to support retirement out of the future earnings of remaining partners ranges from financially dangerous to impossible. Under ideal circumstances of constantly rising income such a plan might be supportable but would still be illogical. If income is increasing it is coming from the increased efforts and heavier work-load of the remaining doctors. To pay out a portion or all of this increase to a retired member would certainly be an injustice to the producing doctors. Like our Social Security system, such a plan under proper circumstances might be supportable on sheer volume of dollars, but it would be completely illogical on economic and moral grounds.

In a recent issue of MEDICAL ECONOMICS, a writer advocated such a plan under the caption, "Let Your Partners Pay For Your Retirement." This article advocated just what the title implies and dwelled exclusively on the possibility of such a plan, ignoring completely any justification for such a plan.

The plan advocated in that article made many erroneous assumptions. Two were most flagrant: (1) that the number of partners would increase constantly, and (2) that the per-doctor income would continue to rise constantly.

Conceding these two premises, it is possible that the plan might function. However, should the profits decline and/or the number of partners decrease, a financial impossibility could result. Another unsound premise involved was the forfeiture of capital and accounts by a doctor leaving voluntarily for reasons other than death or retirement. To summarize: such a plan's success would be solely dependent upon completely favorable financial circumstances; adverse practice and economic conditions could render it wholly unsupportable, except to the ruinous detriment of the remaining partners.

In considering the feasibility of such proposals, you must place yourself in the position of both the retiring and the remaining partner and consider all contingent adversities. If the plan can survive such a test, it may warrant further consideration.

If we agree on the basic premise that a plan must be founded by an investment program and the retiring doctor's contribution to the program, the remaining question is: should such a plan be an individual or a collective responsibility.

In our opinion, unless some specific financial or tax advantage presents itself, partners should provide their own retirement through their individual investment plans. The major problem of a partnership plan is agreeing upon a common medium for investment and the amount to be designated for this purpose. The senior doctors may lean toward an annuity plan with heavy dollar commitments, while younger doctors with already heavy financial burdens would favor a stock or fund purchase plan with lower contributions.

If a tax benefit can be realized, certainly a compromise should be reached, but we would all agree on the imprudence of compromising a financial plan if no such advantage exists. In the absence of this tax advantage, certainly each doctor should pursue his own financial goals.

What are the potential tax benefits available. The prospects of a corporation or association for the two-to-four-man group appear dimmer than at any time in the past. This leaves the Self-Employed Retirement Plan which presently offers only a minimum tax advantage. If and as the law on these plans becomes more favorable, the logic for such plans will increase. However, under present law, these plans offer only a small advantage to those in the right financial situation.

William D. Huntington*
Minneapolis, Minnesota

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*Northern Division Manager, Professional Management Midwest.

Don't you know, as the French say, there are three sexes — men, women, and clergymen. — Sydney Smith

Classified

Classified advertising rates are twenty (20) cents a word; minimum monthly charge $5.00; key number, fifty (50) cents additional.

Replies to advertisements with key numbers should be mailed in care of MINNESOTA MEDICINE, *496 Lowry Medical Arts Bldg., St. Paul, Minn. 55102*

WANTED: General Practitioner who is interested in general practice and surgery to associate with a small group in West Central Wisconsin. Salary and partnership open. Write: MINNESOTA MEDICINE — 349, 496 Lowry Medical Arts Building, St. Paul 55102.

INTERNIST for 20-physician-clinic in prosperous Minnesota city. Salary negotiable first year, then full partnership. East Range Clinic, Virginia, Minnesota.

WANTED: General Practitioners and Pediatrician to join expanding Northwestern Wisconsin 8-man group. New Clinic with full facilities; modern hospitals; excellent school system including the Wisconsin State University; pop. 34,000; early partnership if compatible. Write or call collect R. L. Larson, Mgr., Superior Clinic, Superior, Wis. Phone 715-392-8111.

PART TIME INTERNIST OR GENERAL PRACTITIONER. Good compensation — Midway Area. Alfred F. Anderegg, M.D.; 2500 Como Avenue, St. Paul, Minnesota.

WANTED: Board Certified or eligible internist to associate with group in large, active practice in Minneapolis. Group consists of Surgeon, Obstetrician, Pediatrician and Internist maintaining downtown and suburban offices. Partnership in mind. Contact: Jesse J. Barron, M.D., 1127 Medical Arts Building, Minneapolis, Minnesota 55402, FEderal 2-8259.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with early partnership. Write: MINNESOTA MEDICINE — 289; 496 Lowry Medical Arts Building; St. Paul, 55102.

OFFICE SPACE now available in busy Bloomington. 713 square feet of new space in building with busy group of G.P.'s, dentist and suburban OB-GYN office. Ideal for ophthalmology, ENT or pediatrics. 8040 Penn Avenue South. 888-9211.

WANTED — Internist, board certified or qualified, to associate with two board certified internists. Ten man multi-specialty group. (Lenont Peterson Clinic, Virginia, Minnesota) — Heart of the expanding taconite industry.

FOR RENT: Successful medical building. Will help doctor or group of doctors get started in proven location in Northwest Suburban Minneapolis, 36th and Noble near two hospitals. Call or write Noble Drug, 4705 36th Avenue North, Minneapolis 22. Ju 8-9449.

GENERAL PRACTITIONERS WANTED. City of Lennox, South Dakota offers unusual opportunity immediately for either single practitioners or partnership arrangement. Outstanding financial opportunity for either beginning doctors, or doctors desiring re-location. Exceptionally fine location in prosperous, stable Southeastern South Dakota area offering attractive surroundings, friendly associations, and busy practice with unlimited potentialities. Building available. Inquiries, personal visits welcome. Contact Fred Courey, City Mayor, Lennox, S. Dak.

WANTED: young general practitioner to join six-man group consisting of 4 GPs, a general surgeon, and radiologist. College town of 5,500, 30 miles from Twin Cities. Also need LOCUM TENENS in general practice. Contact: Ed Jenkins, Mgr., River Falls Medical Clinic, River Falls, Wisc. Phone 425-5322.

WANTED: Immediate opening for young GP in an established medical corporation. Three man G.P. group located in rapid-growing North Suburban Metropolitan Area. 15 minutes from loop and large educational center. New clinic. New 150-bed hospital. Salary open, fringe benefits. Fridley Medical Center, P.A., 203 Mississippi Street, Minneapolis, Minnesota 560-2950.

WANTED: Young internist and pediatrician, board certified or eligible, to join 6-man group consisting of 4 GP's, a general surgeon, and a radiologist. College town of 5,500 only 30 miles from Twin Cities. Salary open with early partnership opportunity. Write or call collect: Ed Jenkins, Mgr., River Falls Medical Clinic, River Falls, Wisc., phone 425-5322.

OPENING FOR PHYSICIAN in clinic; general practice; city of 2,000 in northern Minnesota; new 40-bed hospital. Warren Clinic, Warren, Minnesota 56762.

CLINIC LOCATION across from Knollwood and Target Stores. Ample ground and parking space. Will build and lease for interested group, or sell. J. Russell Carroll, 17 Tenth Avenue South, Hopkins, Minnesota. 935-4468.

GENERAL PRACTITIONER, associate, urgently needed. Unopposed practice established 20 years. 32 bed new hospital with additional 20 bed chronic unit. Good anesthesia coverage, lab. facilities. Excellent clinic one block from hospital. Salary with early partnership. Locum tenens also considered. Call collect 218-782-4725 or write Klefstad Clinic, Greenbush, Minnesota.

EXCELLENT DOCTORS' CLINIC available Crystal area — parking and air conditioned — 1500 square feet — will make special rental concession to doctor or doctors interested. Call S. J. Fischman TA 3-3556 or WA 6-2929 in Minneapolis.

OTOLARYNGOLOGIST TO join long established group with possibility of partnership in mid-west area. All instrumentation for entire ear, nose and throat available including the operating microscope. Write: MINNESOTA MEDICINE — 339, 496 Lowry Medical Arts Building, St. Paul 55102.

INTERNIST. Attractive position with six man medical group in northeastern Minnesota. Well equipped thirty-eight bed accredited hospital and two large hospitals in community twenty miles away. Work as consultant on clinic and hospital medical problems. Ideal for physician desiring a small community practice. No investment; full partnership after six months. Contact Community Clinic, Two Harbors, Minnesota.

WANTED — General practitioner to join a busy 3-man group and fill a vacancy left by retirement. Excellent salary first year, followed by full partnership. This progressive central Minnesota town of 2,000 has excellent hospital and clinic facilities, and is in a good farming area containing many lakes. Write: Paynesville Clinic, Paynesville, Minnesota.

THREE MAN Minneapolis GP group desires M.D. with Minnesota license to work during all or some parts of the spring and summer months. Salary open JA 9-9251.

BUSY, GROWING aggressive 3-man partnership in Northwest Wisconsin serving a trade area of 15,000 needs a well-trained recent graduate with fulfilled military obligations to associate immediately on excellent salary, with partnership in 1 year if mutually agreeable. Modern 15 room air conditioned brick clinic building is being doubled in size this year. 32 bed hospital and new 42 bed nursing home one minute from clinic. New 1500 student consolidate school. Excellent hunting, fishing and outdoor sport facilities in immediate area. Contact: MINNESOTA MEDICINE — 317; 496 Lowry Medical Arts Building, St. Paul 55102.

WANTED: Young MD with interest in pediatrics to join established four-man clinic group in Minnesota. Modern clinic building. Members in thirty-six to forty-eight age group. Surgery — OB GYN — Internal Medicine — EENT covered. County seat. Modern hospital. Good hunting and fishing. Excellent eighteen-hole golf course. Progressive farming. Vacation area. Salary open — leading to partnership. Contact: Business Manager, Lake Region Clinic, 1135 Washington Ave., Detroit Lakes, Minnesota.

WANTED: OB-Gyn in well established group in city of 15,000. Good hunting and fishing, we have over 1,000 lakes in county. Excellent hospital and clinic facilities. Write: V. I. Hanson, Business Manager, Park Region Medical Center, Fergus Falls, Minnesota.

GENERAL PRACTITIONER to join general practitioner affiliated with group in neighboring town in northeastern Minnesota. Basically medicine and pediatrics on outpatient basis. Obstetrical and hospital practice optional. Eight days off each month in any mutually agreeable manner plus liberal vacation and study leave. No investment; full partnership after six months. Present doctor spends time in medical missionary work. Age no barrier. Contact Community Clinic, Two Harbors, Minnesota.

RESIDENTS IN PSYCHIATRY — Opening for July 1st 1966 and January 1st 1967. Stipend $11,400 for physicians just completing internship. Federal stipend available to physicians with 4 years nonpsychiatric training or experience following internship amounting to $12,000 annually with an extra $3600 tax exemption. Graduates of American Schools must be eligible for Iowa licensure. Foreign graduates must have ECFWG certificate. Hospital has 450 in-patients, large out-patient dept., children's unit with Board-certified Child Psychiatrist. Eclectic program with emphasis on community and existential psychiatry. Thirteen senior staff members including ten Board certified. Numerous consultants. Authorized for 12 residents. Affiliation with University of Iowa. Enthusiastic and dynamic training and treatment programs that are best understood by a personal visit. Write or call collect: W. C. Brinegar, M.D., Superintendent or John Worthington, M.D., Mental Health Institute, Cherokee, Iowa.

CONTINUALLY GROWING AGGRESSIVE five-man established medical corporation in need of an additional general practitioner. In the group at the present time are three active general practitioners, a board-certified surgeon — well trained, and a board eligible obstetrician and gynecologist. This group is in the northwestern suburban area of Minneapolis with all the financial benefits of an established medical corporation. There is a new 150-bed hospital within five minutes from the clinic office. Please send letter to: Dr. A. H. Mork, Mork Clinic, Anoka, Minnesota if interested in further information.

WANTED AT ONCE — a general practitioner — present physician retiring after 29 years. Opportunity to take over established practice with no obligation. Office space for rent and equipment available. New and accredited community hospital. Full details upon request. Write: Albert J. Emond, M.D., 720 Third Street, Farmington.

PHYSICIAN AVAILABLE. Board surgeon with background general practice and surgery wishes to locate in Twin Cities area. Will also consider locum tenens. Write: MINNESOTA MEDICINE — 352, 496 Lowry Medical Arts Building, St. Paul 55102.

EASTERN WISCONSIN CLINIC in rapidly growing community of 40,000 desires board-eligible or certified physicians in pediatrics, obstetrics and gynecology and internal medicine. Well-equipped clinic and excellent hospital facilities. Lakeshore location offers ample recreational facilities. Attractive financial plan leading to early full partnership. Full expenses paid for applicants invited to interview. Call or write: F. L. Hildebrand, M.D., Riverside Clinic, Menasha, Wisconsin.

GENERAL SURGEON — board certified — 32 — university trained — numerous publications — military completed — one year of surgical practice — desires association or group practice. Cuniculum vitae available. Write: MINNESOTA MEDICINE — 354; 496 Lowry Medical Arts Building 55102.

WANTED INTERNIST to join group in new building with good parking. Salary to start: share earnings later. Other benefits. Write: MINNESOTA MEDICINE — 355; 496 Lowry Medical Arts Building, St. Paul 55102.

GENERAL PRACTITIONER — Well established 14 man multi-specialty group (seven general practitioners) midwestern city, population 30,000. Beginning salary, then partnership; no investment. Clinic building six years old; excellent school, hospital and recreational facilities. Write: MINNESOTA MEDICINE — 356; 496 Lowry Medical Arts Building, St. Paul 55102.

FOR SALE: Mattern X-ray unit. 100 K.V. 60ma. Good for chest and extremity work. Also examining table, instrument cabinet, E.K.G. and other equipment. Contact L. A. Whitesell, Jr., M.D. 207 South First St., Buffalo, Minnesota 55313.

New Issue

The following offering is made by Prospectus only, where state laws permit.

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APACHE MID-YEAR OIL AND GAS PROGRAM 1966

400 PROGRAM UNITS

Offering price:
$10,000 PER UNIT

Also available:
$5,000 PER ½ UNIT

These securities represent pro rata interests in a diversified oil and gas drilling program. They are offered as a speculation.

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Please send me the Prospectus on the Apache Mid-Year Oil and Gas Program 1966.

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Contraindications: In hyperexcitability and in agitated prepsychotic states. Previous allergic or idiosyncratic reactions.

Precautions: Use with caution in patients hypersensitive to sympathomimetic compounds, who have coronary or cardiovascular disease, or are severely hypertensive.

Dextro-amphetamine sulfate: Use by unstable individuals may result in psychological dependence.

Meprobamate: Careful supervision of dose and amounts prescribed is advised; especially for patients with known propensity for taking excessive quantities of drugs. Excessive and prolonged use in susceptible persons, e.g. alcoholics, former addicts, and other severe psychoneurotics, has been reported to result in dependence. Where excessive dosage has continued for weeks or months, reduce dosage gradually. Sudden withdrawal may precipitate recurrence of pre-existing symptoms such as anxiety, anorexia, or insomnia; or withdrawal reactions such as vomiting, ataxia, tremors, muscle twitching and, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, reduce dose—operation of motor vehicles, machinery or other activity requiring alertness should be avoided. Effects of excessive alcohol consumption may be increased by meprobamate. Appropriate caution is recommended with patients prone to excessive drinking. In patients prone to both petit and grand mal epilepsy meprobamate may precipitate grand mal attacks. Prescribe cautiously and in small quantities to patients with suicidal tendencies.

Side Effects: Overstimulation of the central nervous system, jitteriness and insomnia or drowsiness.

Dextro-amphetamine sulfate: Insomnia, excitability, and increased motor activity are common and ordinarily mild side effects. Confusion, anxiety, aggressiveness, increased libido, and hallucinations have also been observed, especially in mentally ill patients. Rebound fatigue and depression may follow central stimulation. Other effects may include dry mouth, anorexia, nausea, vomiting, diarrhea, and increased cardiovascular reactivity.

Meprobamate: Drowsiness may occur and can be associated with ataxia, the symptom can usually be controlled by decreasing the dose, or by concomitant administration of central stimulants. Allergic or idiosyncratic reactions: maculopapular rash, acute nonthrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever, transient leukopenia. A case of fatal bullous dermatitis, following administration of meprobamate and prednisolone, has been reported. Hypersensitivity has produced fever, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, stomatitis, proctitis (1 case), anaphylaxis, agranulocytosis and thrombocytopenic purpura, and a fatal instance of aplastic anemia, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity, usually after excessive dosage. Impairment of visual accommodation. Massive overdosage may produce drowsiness, lethargy, stupor, ataxia, coma, shock, vasomotor, and respiratory collapse.

30
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BAMADEX
DEXTROAMPHETAMINE SULFATE
WITH MEPROBAMATE
SEQUELS
Sustained Release Capsules

First aid for a button popper

Second aid for a button popper

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d-amphetamine sulfate (15 mg.) and meprobamate (300 mg.)
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By providing combined anorexigenic-tranquilizing action, BAMADEX SEQUELS Capsules help your nonshrinking patients to establish new patterns of eating less. The amphetamine component suppresses the appetite, while the meprobamate helps allay nervousness and tension. And for most patients, the *sustained* release of the active ingredients makes possible convenient one-capsule-a-day dosage.

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Sustained circulatory, respirator
and cerebral stimulation for th

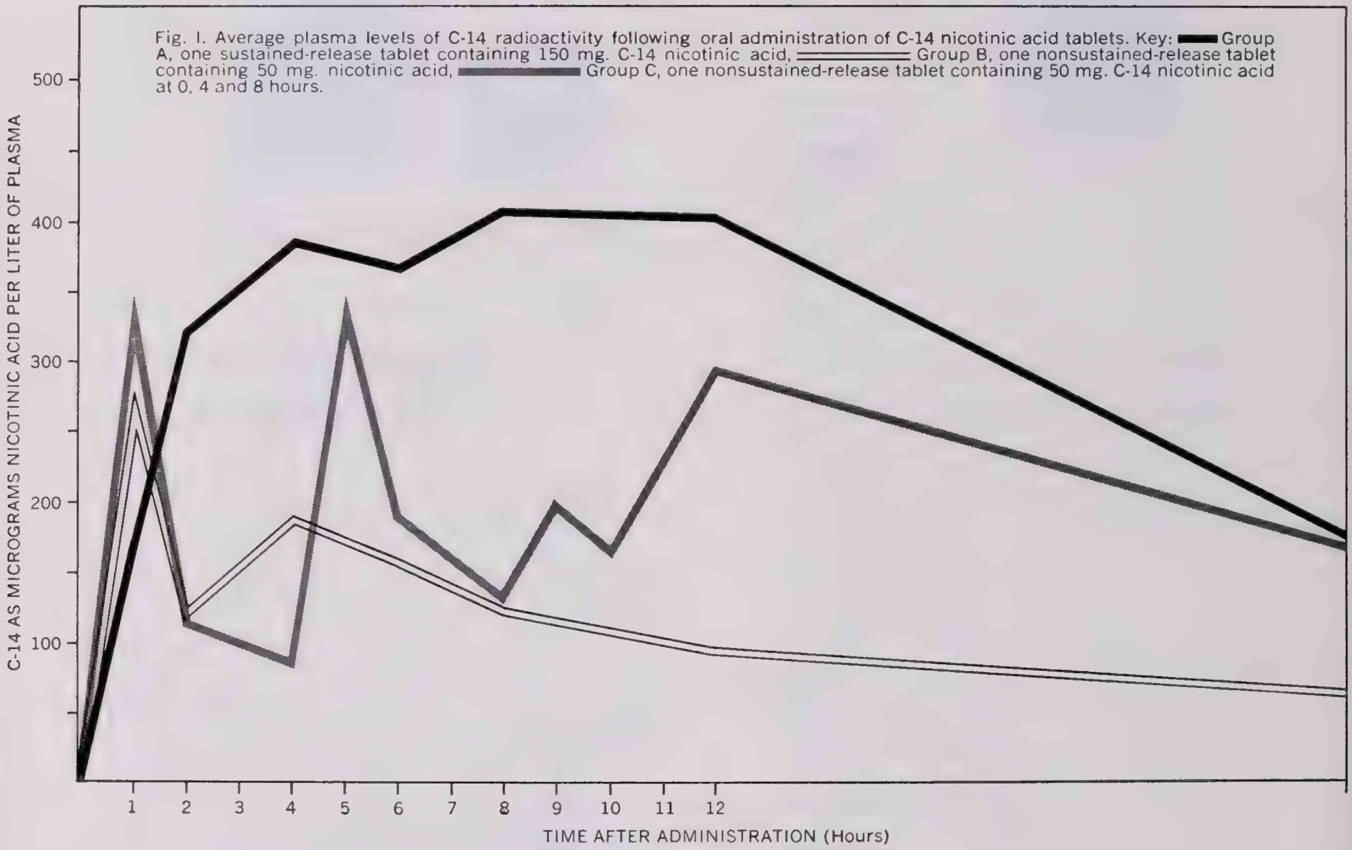

Fig. I. Average plasma levels of C-14 radioactivity following oral administration of C-14 nicotinic acid tablets. Key: ▬ Group A, one sustained-release tablet containing 150 mg. C-14 nicotinic acid, ═ Group B, one nonsustained-release tablet containing 50 mg. nicotinic acid, ▬ Group C, one nonsustained-release tablet containing 50 mg. C-14 nicotinic acid at 0, 4 and 8 hours.

(fewer absent doses by absent-minded patients)

Human volunteer subjects were administered Geroniazol TT tablets with the nicotinic acid component made radioactive with C-14. Plasma and urine samples were analyzed. (See Figures I and II) The radioactive tracer study substantiated the previous clinical evidence that the release of nicotinic acid from the Geroniazol TT tablet produced a gradual rise in plasma levels to a plateau for a total of 12 hours and more.

Such proven sustained activity makes the management of geriatric patients much easier by minimizing the possibility of neglected doses through absent-mindedness or senile confusion. Therapy *can* be continuous on a daily dose of only one Geroniazol TT tablet every 12 hours.

The gradual release of nicotinic acid in Geroniazol TT will provide the well-known peripheral vasodilatation needed in patients with deficient circulation and with a minimum amount (if any) of "flushing." Also, cerebrovascular circulation is complemented by pentylenetetrazol, long-established as a cerebral and respiratory stimulant.

Geroniazol TT improves the typical, unfortunate, signs of senile confusion. Patients become more alert,

ged and debilitated

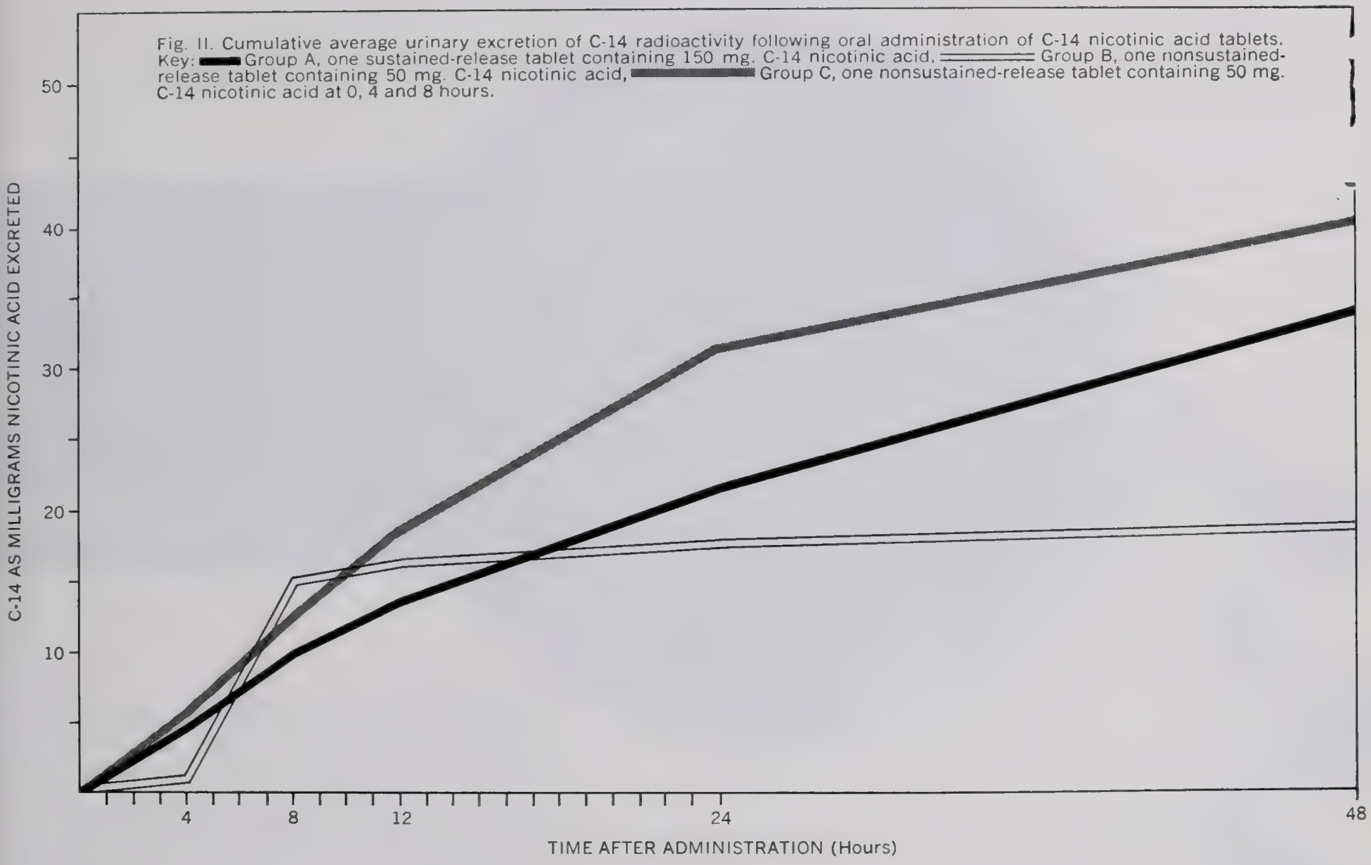

Fig. II. Cumulative average urinary excretion of C-14 radioactivity following oral administration of C-14 nicotinic acid tablets. Key: ▬ Group A, one sustained-release tablet containing 150 mg. C-14 nicotinic acid, ═ Group B, one nonsustained-release tablet containing 50 mg. C-14 nicotinic acid, ▬ Group C, one nonsustained-release tablet containing 50 mg. C-14 nicotinic acid at 0, 4 and 8 hours.

less confused and moody. Personal care, memory, emotional stability, social attention improve. Fatigue, apathy and irritability are reduced.

A prescription for 100 tablets of Geroniazol TT will permit your patients to enjoy the benefits of time-prolonged nicotinic acid/pentylenetetrazol therapy, at an economical price. Dosage is only one tablet every 12 hours.

Contraindications: There are no known contraindications.

Precautions: Exercise caution when treating patients with a low convulsive threshold.

Side Effects: Side effects are rarely encountered, however due to the vasodilatation effect of nicotinic acid, transitory mild nausea, flushing, tingling and pruritus are possible.

Dosage: One tablet every 12 hours.

Supplied: Prescribe bottles of 100 tablets, to take advantage of recent price reduction.

References: 1. Report by Nuclear Science & Engineering Corp., Pittsburgh, Pa., in files of Philips Roxane Laboratories. 2. Connolly, R.: W. Virginia Med. J. *56*:263 (Aug.) 1960. 3. Curran, T. R., and Phelps, D. K.: Am. Pract. & Digest Treat. *11*:617 (July) 1960.

"First with the Retro-Steroids"
PHILIPS ROXANE LABORATORIES
Division of Philips Roxane, Inc., Columbus, Ohio
A Subsidiary of Philips Electronics and
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Geroniazol® TT

nicotinic acid 150 mg., pentylenetetrazol 300 mg.
Tempotrol® Time Controlled Tablet

When uncontrolled diarrhea brings a call for help

When the diarrhea sufferer has run the gamut of home remedies without success, pleasant-tasting CREMOMYCIN can answer the call for help. It can be counted on to consolidate fluid stools, soothe intestinal inflammation, inhibit enteric pathogens, and detoxify putrefactive materials — usually within a few hours.

CREMOMYCIN combines the bacteriostatic agents, succinylsulfathiazole and neomycin, with the adsorbent and protective demulcents, kaolin and pectin, for comprehensive control of diarrhea.

INDICATIONS: Diarrhea.

CONTRAINDICATIONS: Do not use in intestinal obstruction, extensive ulceration of bowel, or diverticulosis; in hypersensitivity to sulfonamides or neomycin; in pregnancy at term, in premature infants, or during first week of life in the newborn.

WARNINGS: Use only after critical appraisal in patients with hepatic or renal damage, urinary obstruction, or blood dyscrasias. Fatal hypersensitivity reactions and blood dyscrasias reported with use of sulfonamides. Consider periodic blood counts, hepatic and renal function tests during intermittent or chronic use.

PRECAUTIONS: Succinylsulfathiazole: Use with caution if there is history of significant allergies and/or asthma. Continued use requires supplementary vitamins B_1 and K. *Neomycin:* Watch for

your ℞ for
Cremomycin
can provide relief

curare-like neuromuscular block during anesthesia if neomycin is used preoperatively in large doses when renal function is poor; watch for overgrowth of nonsusceptible organisms. Consider possibility of ototoxicity and nephrotoxicity with prolonged high dosage.

SIDE EFFECTS: As with all sulfonamides: Headache, malaise, anorexia, G.I. symptoms, hepatitis, pancreatitis, blood dyscrasias, neuropathy, drug fever, rash, conjunctival and scleral injection, petechiae, purpura, hematuria, and crystalluria have been noted. Reduced fecal output of thiamine and decreased synthesis of vitamin K have been reported. *Neomycin:* Nausea, loose stools.

Before prescribing or administering, read package circular with product or available on request.

promptly relieves diarrheal distress

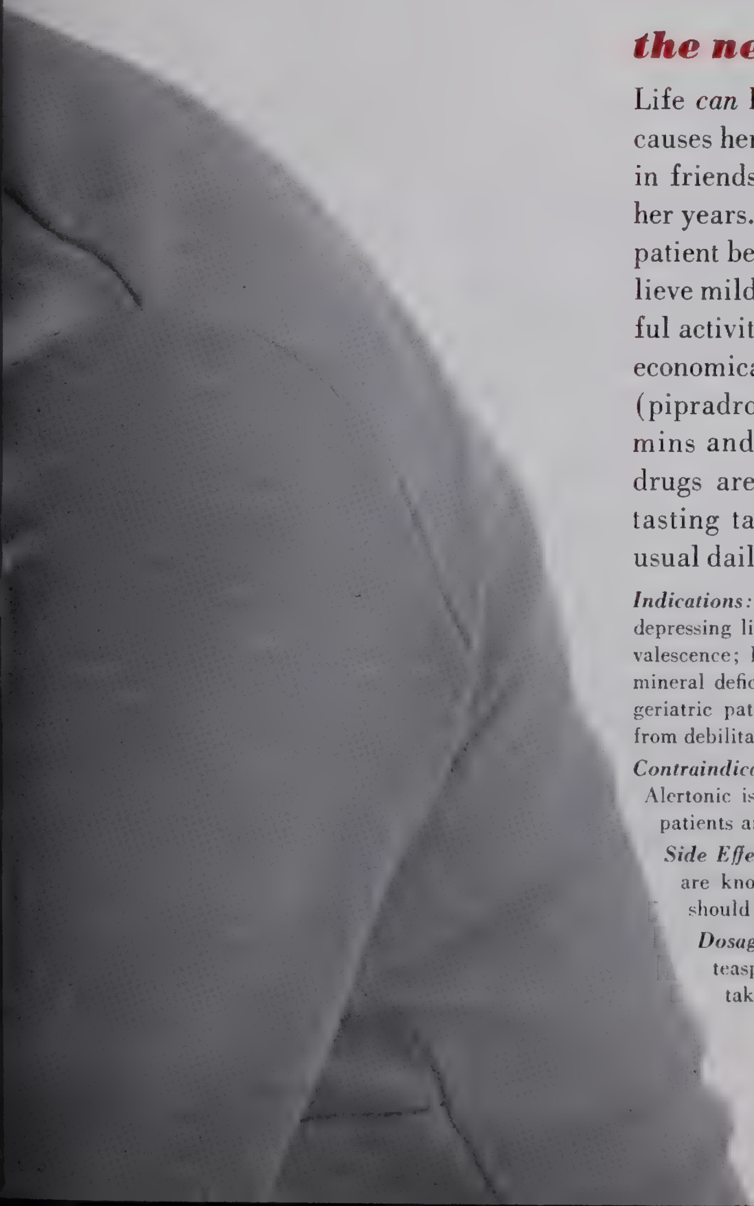
Cremomycin®
ANTIDIARRHEAL

Composition: Each 30 cc. contains neomycin sulfate 300 mg. (equivalent to 210 mg. of neomycin base), succinylsulfathiazole 3.0 Gm., colloidal kaolin 3.0 Gm., pectin 0.27 Gm.

MERCK SHARP & DOHME Division of Merck & Co., Inc., West Point, Pa.

where today's theory is tomorrow's therapy

too young
to be so tired...



revive interest...restore activity promptly with

Alertonic®

Each 45 cc. (3 tablespoonfuls) contains: alcohol, 15%; pipradrol hydrochloride, 2 mg.; thiamine hydrochloride (vitamin B_1) (10 MDR*), 10 mg.; riboflavin (vitamin B_2) (4 MDR), 5 mg.; pyridoxine hydrochloride (vitamin B_6), 1 mg.; niacinamide (5 MDR), 50 mg.; choline†, 100 mg.; inositol†, 100 mg.; calcium glycerophosphate, 100 mg. (supplies 2% MDR for calcium and for phosphorus) and 1 mg. each of the following: cobalt (as chloride), manganese (as sulfate), magnesium (as acetate), zinc (as acetate), and molybdenum (as ammonium molybdate).

*Multiple of adult Minimum Daily Requirement supplied.
†The need for these substances in human nutrition has not been established.

the need for a tonic knows no age

Life *can* begin at forty—except when functional fatigue causes her to feel tired all the time; to start losing interest in friends and surroundings; to look and act older than her years. Alertonic—*a prescription tonic*—can help your patient become her normal self again. Alertonic helps relieve mild depression, revive interest and restore purposeful activity promptly...with a formula that is efficient *and* economical. Alertonic contains a mild central stimulant (pipradrol hydrochloride), 15% alcohol, essential vitamins and minerals. No hormones or MAO-inhibiting drugs are included. No iron. No iodine. One pleasant-tasting tablespoonful before each meal comprises the usual daily dose.

Indications: 1. Functional fatigue such as that often associated with: a depressing life experience or stressful time of life; advancing years; convalescence; limited activity or confinement. 2. Poor appetite and vitamin-mineral deficiency as they occur in: patients having faulty eating habits; geriatric patients who are losing interest in food; patients convalescing from debilitating illness or surgery.

Contraindications: As with other drugs with CNS-stimulating action, Alertonic is contraindicated in hyperactive, agitated or severely anxious patients and in chorea or obsessive-compulsive states.

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Minnesota Medicine at a Glance

Primary Aldosteronism Unmasked — Hawley and Tobian Page 889

A case report of aldosteronism due to adrenal cortical adenoma, in which the clinical symptoms and metabolic alkalosis became evident with the administration of thiazid, points out the possible clinical value of the drug in unmasking an otherwise undiagnosable disease of the adrenal gland.

Hormone-secreting adrenal adenomas may have a variety of histologic appearances and their hormonal functions may be difficult to recognize under the microscope. These tumors can be analyzed for hormone, but the content of the adenoma may not reflect its secretory ability in vivo.

In that the clinical manifestations of primary aldosteronism are usually vague, unless accelerated potassium depletion is effected, the use of thiazide diuretic, as in this instance, will accelerate the potassium depletion and make the diagnosis more evident.

Though the removal of the adrenal tumor effected improvement in the chronic potassium depletion, it did not appreciably affect the hypertension, which was then thought to represent a metacorticoid hypertension similar to that which has been observed in the rat receiving desoxycorticosterone and salt over a long period of time.

Pseudomembranous Enterocolitis — Strickler and Rice Page 899

A review of the literature is presented on pseudomembranous enterocolitis and many associated or related conditions. Staphylococcal enterocolitis is found to be frequently considered as the same disease; but the authors find and record considerable evidence from their review of literature that indicates a definite difference. In essence, staphylococcal enterocolitis may at times produce a pseudomembrane and thus appear similar to pseudomembranous enterocolitis. However, several specific differences in the two conditions are enumerated by the authors.

The case described in this paper, because of its bacteriologic features showing predominantly staphylococci, could be classified in either category. The major point of presentation in this case of advanced pseudomembrane and necrosis is the temporary salvage of the patient by extirpative surgery of nearly all of the colon. Most classical staphylococcic enteritis cases do not advance to this point and are amenable to antibiotic therapy.

Amputation Site — Wessman Page 905

After amputation of a lower extremity the circulation of the stump is subject to the same problems as that of the contralateral extremity. In determining the site of amputation, it is significant that a doctor should make an evaluation of the circulation in the extremity to be amputated, in order for it to be able to tolerate a prosthesis or any other stress that will be applied to it when healing is complete.

When adequate collateral circulation is available below the knee there has usually been a slow onset of the disease process; but when there is an absence of general pulsation, which is frequently observed in patients with cardiac lesions, the collateral circulation has not had time to develop, and an amputation is then indicated above the knee.

Oscillometry, skin thermometry, angiography, and plethysmography are tests that can be made to provide an evaluation of the circulation. Each of these has its special value.

Vision Interference Indicator — Garner and Fulghum Page 909

The authors describe a training device for instructing in the use of the tonometer for measuring intraocular tension. The trainee learns to position himself so that the patient can maintain fixation during measurement of intraocular tension.

Anemia Causing Heart Failure — Searl & Speckhals Page 911

Though iron deficiency anemia is not uncommon in infants, myocardial decompensation resulting from this type of anemia is observed less often. It should be watched for in premature infants showing a rapid growth rate, and when the hemoglobin is found to be at a level of 5 grams, urgent medical measures should be instituted before restoring packed red cells into the circulation.

The response of hemoglobin and reticulocyte count to oral iron therapy is illustrated in the accompanying graph.

Cerebral Vascular Malformation — Neurological Conference Page 961

The case history of a young man with an arterial venous malformation was thoroughly evaluated from all standpoints. After this patient had become stabilized, a successful craniotomy and removal of the arterial venous malformation resulted in his part-time rehabilitation. The interesting details of this case and a complete analysis are reviewed in the neurologic conference.

Servus Naturae

A physician should be the servant of Nature, not her enemy; he should be able to guide and direct her in her struggle for life, and not, by his unreasonable influence, throw fresh obstacles in the way of recovery. . . . The knowledge of Nature is the foundation of the science of medicine.

If you wish to be a true physician you must be able to do your own thinking, and not merely employ the thoughts of others.

The patient must not be out of the physician's mind day or night. He must put his whole power of reasoning and his judgment deliberately in the service of his patients. — Paracelsus (1493-1541)

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O. A. Eide	Hancock
Robert Watson	Morris

SWIFT COUNTY

Joseph Rorem	Appleton
N. Wagner	Benson
T. S. Eberley	Benson

TODD COUNTY

M. E. Mosby	Long Prairie
F. N. Grosse	Clarissa

TRAVERSE COUNTY

A. E. Magnuson	Wheaton
H. C. Winge	Wheaton
Paul T. Vangerud	Wheaton

WABASHA COUNTY

D. W. Sontag	Lake City
W. P. Gjerde	Lake City
R. N. Bowers	Lake City

WADENA COUNTY

L. T. Davis	Wadena
W. E. Parker	Sebeka
W. B. Halme	Wadena

WASECA COUNTY

O. J. Swenson	Waseca
S. T. Normann	Waseca

WASHINGTON COUNTY

R. E. Carlson	Stillwater
J. E. Jenson	Stillwater

WATONWAN COUNTY

A. D. Mattson	St. James
Herbert Boysen	Madelia

WILKIN COUNTY

L. O'Brien	Breckenridge
C. W. Jacobson	Breckenridge
Neil Kippen	Breckenridge

WINONA COUNTY

Herbert vR. Heise	Winona
Robert B. Tweedy	Winona
Henry J. Roemer	Winona

WRIGHT COUNTY

Lester Bendix	Annandale
Pierre J. Guilfoile	Delano

YELLOW MEDICINE COUNTY

C. L. Lundell	Granite Falls
Olin M. Odlund	Granite Falls

Woman's Auxiliary to the Minnesota State Medical Association

Officers

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Mrs. Elwyn Hudec	President-elect	Echo
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Mrs. Theodore Fritsche	Recording Secretary	New Ulm
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Mrs. John H. Peterson	Auditor	Duluth
Mrs. Ralph Olsen	Historian	St. Paul
Mrs. L. P. Howell	Parliamentarian	Rochester

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Mrs. R. T. Petersen	Seventh District	St. Cloud
Mrs. John Rutledge	Eighth District	Detroit Lakes
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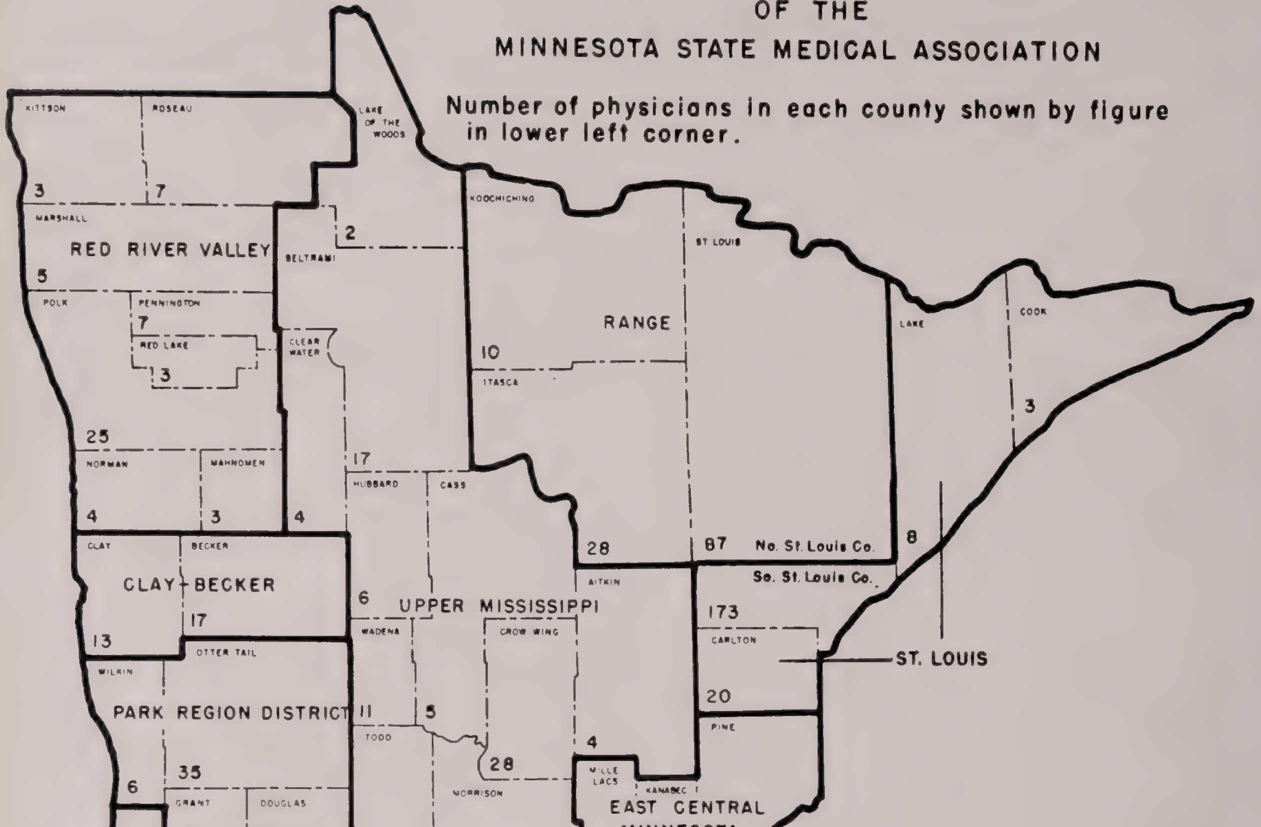
	Mrs. R. F. Erickson	Minneapolis
	Mrs. M. I. Hauge	Clarkfield

COUNTY MEDICAL SOCIETIES
OF THE
MINNESOTA STATE MEDICAL ASSOCIATION

Number of physicians in each county shown by figure in lower left corner.



KITTSON
3
ROSEAU
7
LAKE OF THE WOODS
2
MARSHALL
RED RIVER VALLEY
5
BELTRAMI
POLK
PENNINGTON
7
RED LAKE
3
CLEAR WATER
25
NORMAN
4
MAHNOMEN
3
4
17
KOOCHICHING
10
ITASCA
RANGE
ST LOUIS
28
87
No. St. Louis Co.
So. St. Louis Co.
173
LAKE
8
COOK
3
HUBBARD
CASS
CLAY
BECKER
CLAY-BECKER
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UPPER MISSISSIPPI
AITKIN
WADENA
CROW WING
CARLTON
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ST. LOUIS
OTTER TAIL
WILKIN
PARK REGION DISTRICT
11
5
TODD
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PINE
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GRANT
DOUGLAS
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MORRISON
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MILLE LACS
KANABEC
EAST CENTRAL MINNESOTA
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5
ISANTI
4
TRAVERSE
STEVENS
POPE
WEST CENTRAL MINNESOTA
BIG STONE
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8
STEARNS
STEARNS-BENTON
75
BENTON
6
11
SHERBURNE
4
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CHISAGO
13
ANOKA
23
10
SWIFT
KANDIYOHI
MEEKER
9
KANDIYOHI-SWIFT-MEEKER
WRIGHT
13
WASHINGTON
HENNEPIN
1,214
RAMSEY
555
WASHINGTON
RAMSEY
HENNEPIN
17
CHIPPEWA
LAC QUI PARLE
CAMP RELEASE DISTRICT
14
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16
McLEOD
21
SCOTT
16
CARVER
SCOTT-CARVER
21
DAKOTA
31
YELLOW MEDICINE
16
RENVILLE
RENVILLE-REDWOOD
11
SIBLEY
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LINCOLN
LYON
LYON-LINCOLN
7
16
REDWOOD
12
LE SUEUR
NICOLLET
NICOLLET-LE SUEUR
13
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RICE
30
GOODHUE
31
WABASHA
13
BROWN
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PIPESTONE
MURRAY
COTTONWOOD
SOUTHWESTERN
9
5
15
WATONWAN
9
BLUE EARTH
56
WASECA
7
STEELE
19
DODGE
OLMSTED
ZUMBRO-
7
718
WINONA
31
ROCK
NOBLES
JACKSON
MINNESOTA
6
17
9
MARTIN
FARIBAULT
BLUE EARTH VALLEY
23
18
FREEBORN
30
MOWER
38
FILLMORE
HOUSTON
VALLEY
13
8

County Medical Society Roster

KEY TO SYMBOLS AS FOLLOWS

* Deceased
† Affiliated, Associate, Life, or Resident Members
# Service
‡ Wife is Member of Woman's Auxiliary
¶ Honorary Member

BLUE EARTH COUNTY MEDICAL SOCIETY

Blue Earth County
Regular meetings, Fourth Monday of the month
Annual meeting December
Number of members 59

	PRESIDENT	
	Gislason, Paul H.	Mankato
	SECRETARY	
	Scheidel, A. M.	Mankato
‡	Anderson, Oscar D.	Mankato
‡	Arnesen Paul M.	Mankato
	Batdorf, B. Niles	Mankato
†	Butzer, John A.	Mankato
	Butzer, John F.	Mankato
‡	Chalgren, William S.	Mankato
‡	Conley, Robert H.	Mankato
	Dobson, Mervin W.	Mankato
	Eustermann, John J.	Mankato
‡	Engstrom, Robert B.	Mankato
	Freeman, Donald H.	Mankato
‡	Finch, J. E.	Mankato
	Flentje, Dale E.	Mankato
‡	Florine, Martin C.	Mankato
‡	Fortier, Rene G.	Mankato
†	Franchere, Frederick W.	Lake Crystal
‡	Geurs, Benjamin R.	Mankato
‡	Gislason, Paul H.	Mankato
‡	Goswitz, John T.	Mankato
‡	Hammar, Lawrence M.	Mankato
	Hankerson, Robert G.	Minnesota Lake
‡	Heimark, John J.	Mankato
‡	Heller, Edgar E.	Mankato
‡	Hoeper, Philip G.	Mankato
	Huffington, Herb L.	Waterville
†	Huffington, Herbert L.	Lutsen
	Jones, Orville H.	Mankato
†	Juliar, Richard O.	Los Angeles, California
‡	Kearney, R. Wynn	Mankato
†	Kemp, Alphonse F.	Mankato
	Lester, John W.	Mapleton
‡	Lindblom, Alton E.	North Mankato
†	Luck, Hilda	Mankato
‡	Lund, J. Benjamin	Mankato
	Marso, John L.	Mankato
‡	Mathews, Wallace E.	Mankato
‡	Meredith, Donald C.	Mankato
	Mickelson, John C.	Mankato
†	Miller, Victor I.	Belmont, California
‡	Morgan, Hugh O.	Amboy
‡	Olive, John T., Jr.	Mankato
	Penn, George E.	Mankato
‡	Roth, Frederick D.	Mankato
‡	Sanford, Raymond A.	Mankato
‡	Scheidel, Alois M.	Mankato
‡	Schmitz, Anthony A.	Mankato
‡	Setzer, Hobert J., Jr.	Mankato
‡	Sjoding, J. Donald	Mankato
‡	Smith, Harry J.	Lake Crystal
‡	Snider, Howard R.	Mankato
‡	Snyder, Richard J.	Mankato
	Stillwell, Walter C.	Mankato
‡	Strobel, Claire J.	Mankato
‡	Swenson, Donald B.	Mankato
	Thiem, Chester E.	Mankato
†	Troost, H. Bradley	Mankato
†‡	Vezina, John C.	Mapleton
‡	Von Drasek, Joseph	Mankato
†	Wentworth, Albert J.	Mankato

BLUE EARTH VALLEY MEDICAL SOCIETY

Martin, Watonwan and Faribault Counties
Regular meetings, third Wednesday of each montn
Annual meeting in November
Number of members 42

	PRESIDENT	
	Nickerson, John R.	Fairmont
	SECRETARY	
	Boysen, Herbert	Madelia
‡	Anderson, John W.	Blue Earth
	Armstrong, Ralph S.	Winnebago
	Barr, James S.	Wells
‡	Bellomo, John	Fairmont
†‡	Bergman, Oscar B.	St. James
‡	Boysen, Herbert	Madelia
†‡	Bratrude, Earl J.	Hopkins
	Cox, Russell L.	Estherville, Iowa
	Cullen, Robert M.	Elmore
‡	Drexler, George W.	Blue Earth
‡	Feigal, William M.	Fairmont
‡	Gardner, Jack K.	Fairmont
†‡	Gardner, Victor H.	Fairmont
	Halverson, Donald E.	Winnebago
‡	Halverson, William G.	Madelia
‡	Hanson, Lewis	Frost
‡	Hruza, William J.	Madelia
*†	Hunt, Roscoe C.	Fairmont
	Kraemer, George N.	Fairmont
‡	Krause, Carl W.	Fairmont
‡	Lester, Malcolm J., Jr.	Truman
	Lindahl, Merlyn J.	Sherburn
‡	Mattson, Albert D.	St. James
	Mills, John L.	Winnebago

Continued on Next Page

Blue Earth Valley Medical Society (Continued)

‡	Moulton, Keith B.	St. James
‡	Nickerson, John R.	Fairmont
‡	Nickerson, Neil D.	Fairmont
‡	Ourada, Anthony L.	Fairmont
‡	Parson, R. A.	St. James
	Parsons, Ralph L.	Trimont
‡	Russ, Homer H.	Blue Earth
	Schulz, Robert W.	Fairmont
‡	Smith, Don V.	Blue Earth
‡	Snyder, Clifford D.	Kiester
‡	Thayer, Ellsworth A.	Fairmont
‡	Vaughan, Victor M.	Truman
‡	Virnig, Mark P.	Wells
‡	Virnig, Richard P.	Wells
‡	Wandke, Otto E.	Fairmont
‡	Watkins, John A.	Wells
‡	Williamson, Harold A.	Fairmont
‡	Zemke, Erhart E.	Fairmont
	Zemke, Robert L.	Fairmont

BROWN COUNTY MEDICAL SOCIETY

Brown County
Regular meetings, second Tuesday, January, April, October
Annual meeting in January
Number of members 25

	PRESIDENT	
	Boyle, F. J.	Springfield
	SECRETARY	
	Wohlrabe, Donald E.	Springfield
‡	Black, William A.	New Ulm
‡	Boyle, Francis J.	Springfield
‡	Burnett, Joseph W.	New Ulm
‡	Cairns, Robert J.	Redwood Falls
‡	Carthey, Frank J.	New Ulm
‡	Fesenmaier, Otto B.	New Ulm
†	Fritsche, Albert	New Ulm
‡	Fritsche, Carl J.	New Ulm
‡	Fritsche, Theodore R.	New Ulm
	Goblirsch, Andrew P.	Sleepy Eye
‡	Johnson, Rex R.	New Ulm
‡	Kaiser, Milton L.	New Ulm
‡	Keithahn, Elmer E.	Sleepy Eye
‡	Kitzberger, Peter J.	New Ulm
†	Kusske, Arthur L.	New Ulm
	Muesing, William J.	New Ulm
†	Nuessle, Walter G.	Springfield
‡	Penk, Engward L.	Springfield
	Peterson, Roy A.	Vesta
‡	Rimas, Matthew J.	Comfrey
‡	Ringhofer, Lawrence	New Ulm
‡	Saffert, Cornelius A.	New Ulm
‡	Vogel, Howard A. L.	New Ulm
‡	Wohlrabe, Donald E.	Springfield
‡	Wohlrabe, Edwin J.	Springfield

CAMP RELEASE DISTRICT MEDICAL SOCIETY

Chippewa, Lac qui Parle and Yellow Medicine Counties
Regular meetings, third Thursday of each month
except July and August
Annual meeting, November
Number of members 26

	PRESIDENT	
	Anderson, C. A.	Madison
	SECRETARY	
	Hagberg, Norman L.	Montevideo
‡	Allen, John H.	Montevideo
	Anderson, Chester A.	Madison
	Birkey, Thomas G.	Montevideo
‡	Boody, George J., Jr.	Cambridge
‡	Burns, Floyd M.	Milan
†	Burns, M. A.	Milan
‡	Camp, Ray J	Madison
†	Fallon, Virgil T.	Minneapolis
‡	Gustafson, Robert W.	Granite Falls
‡	Hagberg, Norman L.	Montevideo
†‡	Hauge, Malvin I.	Clarkfield
†	Holmberg, LeRoy J.	Canby
*‡	Hudec, Elwyn R.	Echo
‡	Johnson, Vilhelm M.	Dawson
†	Jordan, Kathleen B. Smith	Granite Falls
*	Jordan, Lewis S.	Granite Falls
†‡	Kaufman, William C.	Appleton
‡	Kremer, Jerome L.	Montevideo
‡	Lima, Ludvig R.	Montevideo
‡	Lundell, Carl L.	Granite Falls
‡	Maus, Philip W.	Dawson
‡	Niazi, Suad A.	Granite Falls
‡	Odland, Olin M.	Granite Falls
‡	Owens, William A.	Montevideo
*†	Pertl, Albert L.	Canby
‡	Radke, Robert L.	Montevideo
‡	Roust, Henry A.	Montevideo
‡	Schmidt, Paul G.	Granite Falls
‡	Westby, Norval M.	Madison

CLAY-BECKER COUNTY MEDICAL SOCIETY

Clay and Becker Counties
Regular meetings, three per year
Annual meeting, December
Number of members 28

	PRESIDENT	
	Knapp, James F.	Detroit Lakes
	SECRETARY	
	Saxman, Gertrude	Ulen
	Bigler, Earl E.	Perham
	Bigler, Ivan E.	Perham
	Bologna, Camillo V.	Moorhead
†	Bottolfson, B. T.	Moorhead
‡	Brenk, Paul E.	Detroit Lakes
‡	Carlon, Donald L.	Moorhead
‡	Carlson, Vernon J.	Moorhead
‡	Dodds, William C.	Detroit Lakes
‡	Duncan, James W.	Moorhead
‡	Geib, Marvin J.	Fargo, North Dakota
*†	Hagen, Olaf J.	Moorhead
‡	Holten, John	Moorhead
	Johnson, Olga H.	Moorhead
‡	Knapp, James F.	Detroit Lakes
	Koons, William R.	Mahnomen
†	Larson, Arnold	Detroit Lakes
‡	Lorentzen, Ernest S.	Detroit Lakes
‡	Midthune, Andreen S.	Lake Park
‡	Moberg, Clarence W.	Detroit Lakes
	Odland, Mark E.	Detroit Lakes
‡	Rice, Hagbart G.	Moorhead
‡	Rutledge, John B.	Detroit Lakes
†‡	Rutledge, Lloyd H.	Detroit Lakes
	Saxman, Gertrude E.	Ulen
‡	Simison, Carl	Barnesville
‡	Thysell, Vernon D.	Moorhead
‡	Watson, Robert N.	Detroit Lakes
‡	Watson, Virgil A.	Detroit Lakes

EAST CENTRAL MINNESOTA MEDICAL SOCIETY

Anoka, Chisago, Isanti, Kanabec, Mille Lacs, Pine and Sherburne Counties
Regular meetings first Tuesday of even months of the year
Annual meeting First Tuesday in December
Number of members 40

	PRESIDENT	
	Lindquist, Dale C.	Lindstrom
	SECRETARY	
	Sommer, Robert K.	Elk River
*‡	Adkins, Galen H.	Cambridge
	Ahlstrom, Robert C.	Braham
	Aruguete, Alayne	Sandstone
	Aruguete, Jose	Sandstone
‡	Berglund, Alvin E.	Cambridge
	Bunker, Bevan W.	Anoka
‡	Burseth, Edgar C.	Mora
	Courteau, Robert D.	Onamia
‡	Deason, Keith B.	Chisago City
‡	Dittrich, R. J.	Anoka
	Doebler, Myron I.	Mora
	Gailitis, Veronika M.	St. Paul
	Grinvalds, Anna O.	Cambridge
	Halpin, Joseph E.	Rush City
‡	Hilgedick, William R.	Chisago City
‡	Hovde, Gordon W.	Chisago City
	Huber, Robert W.	St. Croix Falls, Wis.
	Johnson, Aldridge F.	St. Paul
‡	Kapsner, Alfred	Princeton
†	Kelsey, Carleton G.	St. Paul
‡	Larson, Gerald E.	Cambridge
‡	Lindquist, Dale C.	Lindstrom
‡	McManus, William F.	Princeton
	Mach, Ralph F.	Pine City
‡	Magnuson, Raymond C.	Cambridge
	Metcalf, Norman B.	Princeton
	Nelson, Luther A.	Rush City
‡	Nordman, Willard F.	Mora
	Popovich, Dragojla	Milwaukee, Wis.
‡	Roehlke, Arthur B.	Elk River
‡	Sander, John L.	Cambridge
†	Schut, John W.	Minneapolis
‡	Seecamp, Carsten H.	Cambridge
	Sommer, Robert K.	Elk River
	Spurzem, Raymond J.	Anoka
‡	Swenson, Roy G.	North Branch
‡	Tesch, Gordon H.	Elk River
	Textor, Jerome	Anoka
‡	Travis, Richard C.	Elk River
†	Waller, Joseph D.	Pine City

FREEBORN COUNTY MEDICAL SOCIETY

Freeborn County
Regular meetings, third Thursday of each month
Annual meeting, December
Number of members 35

	PRESIDENT	
	Blumer, A. R.	Albert Lea
	SECRETARY	
	Ellertson, Leonard M.	Albert Lea
	Arnold, Arthur L.	Albert Lea
‡	Barr, Lowell C.	Albert Lea
‡	Barr, Lowell W.	Albert Lea
‡	Bartness, John E.	Albert Lea
‡	Blumer, Arlo R.	Albert Lea
‡	Bryant, Emmett P.	Ellendale
†	Burns, Catherine	Excelsior
*†	Butturff, Carl R.	Freeborn
†	Calhoun, Frank W.	Albert Lea
‡	Campbell, John C.	Albert Lea
	Cole, George A.	Albert Lea

Continued on Next Page

Freeborn County Medical Society (Continued)

‡	Demo, Robert A.	Albert Lea
‡	Donovan, Daniel L.	Albert Lea
‡	Egge, Sanford G.	Albert Lea
‡	Ellertson, Leonard M.	Albert Lea
†	Freeman, John P.	Glenville
‡	Gamble, Elbert J.	Albert Lea
‡	Gill, Theodore M.	Albert Lea
‡	Hansen, Theodore M.	Albert Lea
‡	Holian, Darwin K.	Albert Lea
*†	Kassa, Lawrence J.	Albert Lea
‡	Keil, Marcus A.	Albert Lea
†	Leopard, Brand A.	Brownsville, Texas
‡	Menefee, Edward C.	Albert Lea
‡	Myers, Theodore P.	Albert Lea
‡	Neel, Harry B.	Albert Lea
‡	Nelson, Clayton E. J.	Albert Lea
‡	Nesheim, Martin O.	Emmons
‡	Palmer, Clinton F.	Albert Lea
‡	Schmidt, Ruben F.	Alden
‡	Sherman, Alfred G.	Albert Lea
‡	Steiner, Leon E.	Albert Lea
‡	Stoker, Lynn C.	Albert Lea
‡	Whitson, Sidney A.	Albert Lea
‡	Wilcox, G. Charles	Albert Lea

GOODHUE COUNTY MEDICAL SOCIETY

Goodhue County
Regular meeting, May
Annual meeting, October
Number of members 25

	PRESIDENT	
	Billings, Harry H.	Red Wing
	SECRETARY	
	Rayner, Ralph R.	Red Wing
*†	Aanes, Almer M.	Red Wing
‡	Akins, Willard M.	Red Wing
‡	Billings, Harry H.	Red Wing
‡	Brusegard, James F.	Red Wing
‡	Cant, Wilbur F.	Red Wing
‡	Delahunty, John R.	Red Wing
	Douglass, Jesse E.	Cannon Falls
	Falls, John L.	Red Wing
	Friedrich, Bradford E.	Red Wing
†‡	Graves, Richard B.	Red Wing
‡	Halvorson, James W.	Zumbrota
‡	Hartnagel, Grant F.	Red Wing
‡	Hawley, George M. B., II	Red Wing
‡	Jackish, George E.	Red Wing
‡	Juers, Edward H.	Red Wing
‡	Larson, Oliver E. H.	Zumbrota
‡	Molenaar, Robert E.	Cannon Falls
	Nicolay, William R.	Red Wing
‡	Rayner, Ralph R.	Red Wing
‡	Shepard, Richard	Red Wing
‡	Sherman, Royal V.	Red Wing
†	Smith, Myron W.	Red Wing
‡	Steffens, Leon A.	Red Wing
‡	Walter, William E.	Wanamingo
‡	Wasmund, Clarence W.	Red Wing
‡	Williams, Marland R.	Cannon Falls

HENNEPIN COUNTY MEDICAL SOCIETY

Hennepin County
Regular meetings, first Monday of the Months of
October, January, March and May, except when
otherwise designated
Annual meeting, first Monday in October
Number of members 1301

	PRESIDENT	
	Frey, Richard J.	Minneapolis
	SECRETARY	
	Chisholm, Tague C.	Minneapolis
	EXECUTIVE SECRETARY	
	Cook, Thomas P.	Minneapolis
‡	Abramson, Burton I.	Minneapolis
	Abramson, Milton	Minneapolis
‡	Abullarade, Jose A.	Minneapolis
	Adams, Richard I.	Minneapolis
	Adcock, Leon L.	Minneapolis
‡	Adkins, C. Douglas	Minneapolis
‡	Agustsson, Hreidar	Minneapolis
‡	Ahern, Eugene E.	Minneapolis
	Alari, Heino	Excelsior
‡	Alexander, Harlan A.	Minneapolis
‡	Aling, Charles A.	Minneapolis
‡	Allen, James R.	Minneapolis
	Alter, Milton	Minneapolis
†	Altnow, Hugo O.	Coral Gables, Florida
‡	Amatuzio, Donald S.	Minneapolis
‡	Amren, Don P.	Minneapolis
	Anderegg, Alfred F.	St. Paul
‡	Andersen, James G.	Minneapolis
‡	Anderson, Arnold S.	Minneapolis
	Anderson, Ben H.	Minneapolis
‡	Anderson, David M.	Minneapolis
†	Anderson, Edward D.	Vaud, Switzerland
‡	Anderson, Ernest R.	Minneapolis
‡	Anderson, Frank J.	Minneapolis
	Anderson, John A.	Minneapolis
‡	Anderson, Karl W.	Excelsior
	Anderson, Richard W.	Minneapolis
	Anderson, Roger E.	Minneapolis
‡	Anderson, Roger L.	Minneapolis
	Anderson, Thomas P.	Minneapolis
‡	Anderson, U. Schuyler	Fargo, North Dakota
	Anderson, Wallace E.	Minneapolis
‡	Anderson, Wallace R.	Minneapolis
‡	Anderson, William H.	Minneapolis
	Anderson, William T.	Minneapolis
	Anderson, W. Robert	Minneapolis
†	Andreassen, Einar C.	Minneapolis
‡	Andreassen, Rolf L.	Minneapolis

Hennepin County Medical Society (Continued)

‡	Andreasen, Karl d'A	Minneapolis
‡	Ankner, Frank J.	Minneapolis
‡	Anonsen, Richard E.	Minneapolis
	Anselment, Lois A.	Excelsior
†	Arends, Archabald L.	Minneapolis
‡	Arey, Stuart Lane	Minneapolis
‡	Arhelger, Stuart W.	Minneapolis
‡	Arlander, Clarence E.	Minneapolis
‡	Arling, Leonard S.	Minneapolis
‡	Arms, James J.	Minneapolis
	Armstrong, Byron H.	Minneapolis
	Arnold, Ann W.	Minneapolis
	Arnold, Thomas B.	Minneapolis
*†	Arvidson, Carl G.	Minneapolis
‡	Aughenbaugh, John W.	Minneapolis
	Azad, A. M.	Minneapolis
‡	Baggenstoss, Osmond J.	Minneapolis
‡	Bagley, Russell W.	Minneapolis
‡	Baken, Melvin P.	Minneapolis
‡	Baken, Melvin P., Jr.	Minneapolis
	Baker, Abe B.	Minneapolis
†	Baker, Alfred T.	Minneapolis
‡	Baker, C. Camak	Minneapolis
‡	Baker, Milton E.	Minneapolis
	Bakke, Arnold C.	Minneapolis
‡	Baleisis, Peter	Minneapolis
‡	Balkin, Samuel G.	Minneapolis
‡	Balogh, Charles J.	Minneapolis
	Bank, Harry E.	Minneapolis
‡	Barnett, Robert M.	Minneapolis
‡	Barno, Alex	Minneapolis
‡	Barr, Maxwell M.	Minneapolis
	Barr, Robert M.	Minneapolis
	Barrett, Patrick J.	Minneapolis
	Barron, Jesse J.	Minneapolis
†‡	Barron, Moses	Beverly, Hills, Calif
	Barry, George J.	Minneapolis
	Beach, Northrop	Minneapolis
	Beard, Archibald H., Jr.	Minneapolis
‡	Beirstein, Samuel	Minneapolis
	Beiswanger, Richard H.	Minneapolis
‡	Bell, Donald C.	Minneapolis
‡	Bellville, Titus P.	Minneapolis
‡	Belzer, Meyer S.	Minneapolis
	Benesh, Louis A.	Minneapolis
‡	Benjamin, Edwin G.	Minneapolis
‡	Benjamin, Harold G.	Minneapolis
	Benjamin, Richard D.	Minneapolis
‡	Benjamin, Robert B.	Minneapolis
	Bentz, Herman D.	Anoka
‡	Berestka, Stephen J.	Minneapolis
	Berg, Clinton C.	Excelsior
	Berger, Alex G.	Minneapolis
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	Bergh, Solveig M.	Minneapolis
‡	Berglund, Eldon B.	Minneapolis
‡	Bergquist, James R.	Minneapolis
‡	Berkwitz, Nathaniel J.	Minneapolis
	Berman, David A.	Minneapolis
	Berman, Reuben	Minneapolis
	Bernstein, Irving C.	Minneapolis
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‡	Berry, Ronald N.	Minneapolis
‡	Bessesen, Alfred N.	Minneapolis
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	Bieter, Raymond N.	Minneapolis
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	Bittick, Wilbur H.	Minneapolis
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‡	Blake, James A.	Hopkins
‡	Blake, Paul S.	Minneapolis
	Blaw, Michael E.	Minneapolis
	Bloch, Henry S.	Minneapolis
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‡	Blomberg, Robert D.	Minneapolis
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	Bloom, Norman B.	Minneapolis
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‡	Bohn, Donald G.	Minneapolis
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	Bouthilet, Florence J.	Minneapolis
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‡	Bowlin, Paul F.	Minneapolis
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	Bradley, John G.	Minneapolis
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*†‡	Bratrud, Arthur F.	Minneapolis
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‡	Brauti, E. Fred	Corvallis, Oregon
	Breitenbucher, Robert B.	Minneapolis
‡	Brekke, Harvey J.	Minneapolis
‡	Brennan, Joseph G.	Minneapolis
	Brill, Alice K.	Minneapolis
‡	Briones, Bienvenido R.	Hopkins
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	Brown, William D.	Minneapolis
	Brown, William D., Jr.	Minneapolis
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	Buckley, Joseph J.	Minneapolis
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	Burgess, Glenn N.	Anoka
	Burkholder, Dayton D.	Anoka
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	Bush, Roger A.	Minneapolis
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‡	Calin, S. Hartley	Minneapolis
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	Cardle, James G.	Minneapolis
‡	Cardle, John B.	Minneapolis
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	Carlson, Robert G.	Anoka
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Hennepin County Medical Society (Continued)

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‡	Cella, Joseph A.	Minneapolis
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	Challman, S. Alan	Minneapolis
	Chandler, William M.	Minneapolis
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‡	Chesler, Merrill D.	Minneapolis
	Child, Sherman B.	Minneapolis
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	Chou, Shelley N.	Minneapolis
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	Christenson, Leland R.	Maple Plain
	Clark, Malcolm D.	Minneapolis
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	Clark, W. Bruce	Minneapolis
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	Cochrane, Ray F.	Minneapolis
	Coe, John I.	Minneapolis
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	Cohen, Ephraim B.	Minneapolis
	Cohen, Henry W.	Wayzata
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‡	Cooper, Robert R.	Minneapolis
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	Dahl, James C.	Minneapolis
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	Dargay, Cyril P.	Minneapolis
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	Davis, Eunice A.	Bismarck, N. D.
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‡	Davis, Michael W.	Minneapolis
	Dawson, Walter J., Jr.	Minneapolis
	Dedeker, Kenneth L.	Minneapolis
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	Dickman, Roy W.	Minneapolis
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	Docherty, John A.	Anoka
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	Dornbach, Robert A.	Minneapolis
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‡	Dorsey, William E.	Minneapolis
	Doscherholmen, Alfred	Minneapolis
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‡	Dredge, Thomas E., Jr.	Minneapolis
	Drill, Frederick E.	Minneapolis
‡	Drill, Herman E.	Hopkins
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	Duffell, David R.	Minneapolis
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	Duncan, Donald A.	Minneapolis
‡	Dunlap, Earl H.	Minneapolis
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	Duryea, Marbry	Minneapolis
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‡	Duryea, Willis M., Jr.	Minneapolis
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	Earl, Stephan H.	Minneapolis
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	Eich, Matthew A.	Minneapolis
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	Eisenstadt, David H.	Minneapolis
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	Eitel, George D.	Minneapolis
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	Emond, Albert J.	Farmington
	Emond, Joseph S.	Farmington
	Emond, Joseph S., Jr.	Minneapolis
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‡	Engstrom, E. Duane	Minneapolis
	Engwall, Richard L.	Minneapolis
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	Farley, Harrison H.	Minneapolis
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	Fetzek, Albert D	Minneapolis

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‡	Fink, Robert J.	Minneapolis
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	Freeman, Donald W.	St. Louis Park
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	Friberg, Joseph B.	Minneapolis
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	Friedell, George	Minneapolis
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	Frost, Russell H.	Fargo, No. Dak.
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	Frys, Russell N.	Minneapolis
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	Furman, L. Christine	Minneapolis
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	Galbraith, Richard F.	Minneapolis
	Galejs, Aina	Minneapolis
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	Garetz, Floyd K.	Minneapolis
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	Garten, Joseph L.	Minneapolis
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	Gault, Neal L., Jr.	Minneapolis
	Gault, Sarah Jane	Minneapolis
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‡	Geller, Joseph	Minneapolis
‡	George, Vane P., Jr.	LeSueur
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	Giere, Richard W.	Minneapolis
	Gilbert, Maurice G.	Minneapolis
	Gilbertsen, A. Sigrid	Minneapolis
	Gilbertsen, Victor A.	Minneapolis
	Gilles, Paul J.	Minneapolis
	Gingold, Benjamin A.	Minneapolis
	Glaeser, John H.	Minneapolis
‡	Godfrey, H. Wilson	Minneapolis
	Goetz, Frederick C.	Minneapolis
	Gokcan, Muharrem	Minneapolis
	Gokcen, Barbara W.	Minneapolis
‡	Gold, David	Minneapolis
‡	Goldberg, Isadore M.	Minneapolis
	Goldberg, Marvin E.	Minneapolis
‡	Goldberg, Stanley M.	Minneapolis
	Goldfarb, Benjie L.	Minneapolis
	Goldfarb, Mace G.	Minneapolis
	Goldman, Leonard W.	Minneapolis
‡	Goldman, Theodore I.	Minneapolis
‡	Goldner, Meyer Z.	Minneapolis
	Goldstein, Alan L.	Hopkins
‡	Good, Gary	Minneapolis
	Goodchild, William R.	Minneapolis
	Gordon, John R.	Minneapolis
	Gordon, Philip E.	Long Lake
‡	Gordon, Sewell S.	St. Louis Park
‡	Granquist, Richard D.	Minneapolis
	Grant, Suzanne	Minneapolis
†	Gratzek, Frank R.	Anoka
	Gray, Royal C.	Minneapolis
	Green, Clayton R.	Excelsior
	Green, Robert A.	St. Louis Park
‡	Greenberg, Albert J.	Minneapolis
	Greene, Leonard H.	Minneapolis
‡	Greenfield, Irving	Minneapolis
†	Greisheimer, Esther M.	Philadelphia, Pa.
	Grimes, Marian	Minneapolis
‡	Grimmell, Francis J.	Minneapolis
‡	Grismer, Jerome T.	Minneapolis
†	Gronvall, Paul R.	Minneapolis
‡	Grotting, John K.	Minneapolis
	Gruys, Robert I.	Wells
‡	Gullickson, Glenn, Jr.	Minneapolis
‡	Gunlaugson, Frederick G.	Minneapolis
‡	Gustafson, Paul O.	Minneapolis
‡	Gustason, Harold T.	Minneapolis
	Gustilo, Ramon B.	Minneapolis
	Haas, John W.	Minneapolis
	Haberer, Helen R.	Minneapolis
‡	Haberle, Charles A.	Minneapolis
‡	Hagen, Kristofer	Minneapolis
‡	Hagen, Wayne S.	Minneapolis
	Haglin, John J.	Minneapolis
‡	Hall, Harry B.	Minneapolis
‡	Hall, Wendell H.	Minneapolis
	Hallin, Roger P.	Minneapolis
‡	Hambidge, Gove, Jr.	Minneapolis
‡	Hamel, Arnold L.	Minneapolis
‡	Hamel, Joseph I.	Minneapolis
	Hammerstrom, Robert N.	Minneapolis
	Handler, Seymour	Minneapolis
‡	Hannah, Hewitt B.	Minneapolis
‡	Hansen, Cyrus O.	Minneapolis
†‡	Hansen, Erling W.	Minnetonka
†	Hansen, Olga S.	Minneapolis
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†	Hanson, Harlow J.	Minneapolis

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Hennepin County Medical Society (Continued)

	Hanson, Harold B.	Minneapolis
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†	Hanson, Henry V.	St. Paul
†‡	Hanson, Malcolm B.	Osseo
	Hanson, Mark C. L.	Minneapolis
	Hanson, Mildred S.	Minneapolis
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‡	Hanson, William B.	Minneapolis
	Happe, Lawrence J.	Minneapolis
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	Hartman, Evelyn E.	Minneapolis
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	Haugen, John A.	Minneapolis
	Hauser, Donald C.	Minneapolis
†	Hauser. George W.	Seattle, Washington
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‡	Hays, Albert T.	Minneapolis
‡	Haywa, E. William	Minneapolis
‡	Head, Douglas P.	Minneapolis
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‡	Hedrick, William L.	Minneapolis
‡	Hempel, Dean J.	Minneapolis
‡	Henrikson, Earl C.	Minneapolis
	Herbert, Willis L.	Minneapolis
	Hermann, Harold W.	Minneapolis
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	Hiatt, John A.	Minneapolis
	Hickok, David F.	Minneapolis
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‡	Hoffert, Henry E.	Minneapolis
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‡	Hoffman, Walter Lees	Minneapolis
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	Horns, Norman	Minneapolis
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‡	Hoseth, Wayne L.	Minneapolis
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‡	Houle, Rollin J.	New Brighton
	Hovland, Melvin L.	Minneapolis
	Hovland, Richard D.	Minneapolis
‡	Howard, Robert B.	Minneapolis
	Howard, Solomon E.	Minneapolis
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‡	Hoyt, C. Sherman	Minneapolis
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	Huff, John S.	Minneapolis
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	Hultkrans, Rudolph E.	Minneapolis
‡	Hurr, Maland C.	Minneapolis
	Hustad, Edward G.	Minneapolis
‡	Hymes, Charles	Minneapolis
	Ide, Arthur W., Jr.	Minneapolis
‡	Idstrom, Linneus G.	Minneapolis
‡	Indeck, Walter	Minneapolis
	Ingalls, Edgar G.	Minneapolis
	Iverslie, Philip C.	Minneapolis
	Iverson, Eleanor B.	Minneapolis
‡	Iverson, Rolf M.	Minneapolis
‡	Jackson, J. Albert	Minneapolis
	Jackson, Richard L.	Minneapolis
‡	Jacobson, Leslie W.	Minneapolis
‡	Jacobson, Loren J.	Minneapolis
	Jacobson, Wyman E.	St. Louis Park
‡	Jaffe, Manuel O.	Minneapolis
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	Janecek, James, Jr.	Minneapolis
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	Jensen, Paul A.	Minneapolis
	Jensen, Reynold A.	Minneapolis
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	Jerome, Bourne	Minneapolis
	Jerome, Elizabeth B. K.	Minneapolis
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‡	Johnson, Donald A.	Minneapolis
	Johnson, Edward A.	Minneapolis
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	Johnson, Gordon E.	Minneapolis
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	Johnson, Norman P.	Minneapolis
	Johnson, Norman Paul	St. Paul
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	Johnson, Thomas G., Jr.	Minneapolis
	Johnson Youbert T.	Minneapolis
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	Jorgensen, Harlan	Minneapolis
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	Jurdy, Mitchell J.	Minneapolis
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	Kaiser, Harold B.	Minneapolis
	Kalb, Thomas J.	Minneapolis
‡	Kallestad, Leonard L.	Wayzata
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	Kantar, Bruce L.	Minneapolis
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‡	Kaplan, J. Jacob	Minneapolis

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	Katz, Beni	Minneapolis
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‡	Kelly, John C.	Minneapolis
‡	Kelly, John P.	Minneapolis
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	Kennedy, Byrl J.	Minneapolis
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	Kennedy, William R.	Minneapolis
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	King, Frances W.	Minnetonka
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	Kitchen, Clyde K.	Minneapolis
	Kjos, Ronald K.	Anoka
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	Knobloch, William H.	Minneapolis
	Knudsen, Helen L.	Minneapolis
	Kohlhase, Robert E.	Minneapolis
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†‡	Koller, Louis R.	Minneapolis
‡	Koller, Robert L.	Minneapolis
	Koos, Gerald W.	Minneapolis
	Korchik, John P.	Minneapolis
	Kottke, Frederic J.	Minneapolis
	Koucky, Rudolph W.	Minneapolis
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	Kozak, Michael J.	Minneapolis
‡	Krafft, Walter E.	Minneapolis
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‡	Kremen, Arnold J.	Minneapolis
	Krieser, Albert E.	Minneapolis
	Krystosek, Lee A.	Minneapolis
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†	Kucera, William J.	Santa Barbara, California
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	LaBree, John W.	St. Louis Park
‡	Lagaard, Sheldon M.	Minneapolis
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	Langer, Leonard O., Jr.	Minneapolis
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	Larson, Leland J.	Minneapolis
	Larson, Leonard M.	Minnetonka
	Larson, Loren J.	Minneapolis
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‡	Larson, Richard E.	Minneapolis
	Larson, Roger C.	Minneapolis
	Larson, Wyllis G.	Minneapolis
	Latts, Elliot M.	Minneapolis
†	LaVake, Rae T.	Minneapolis
	Lawrence, Van S.	Minneapolis
	Lawrow, John W.	Minneapolis
	Lawson, Warren R.	Minneapolis
‡	Lawton, James J., Jr.	Minneapolis
	Laymon, Carl W.	Minneapolis
‡	Leavenworth, Richard O., Jr.	Minneapolis
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	Lees, David C.	Minneapolis
‡	Leiferman, Robert J.	Minneapolis
	Leighton, John S.	Minneapolis
	Leinonen, Wendla E.	Anoka
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‡	Lenz, Oa	Minneapolis
†‡	Leonard, Lawrence J.	Minneapolis
‡	Leonard, Samuel	Minneapolis
	Lerner, A. Ross	Minneapolis
‡	Leslie, Loren R.	Minneapolis
	Leslie, W. Robert	Minneapolis
‡	Lester, Theodore H.	Minneapolis
‡	Levine, Howard M.	Minneapolis
‡	Lick, Louis C.	Minneapolis
	Lienke, Roger I.	Robbindale
	Lillehei, C. Walton	Minneapolis
‡	Lillehei, Richard C.	Minneapolis
‡	Limbeck, Donald A.	Minneapolis
‡	Lindberg, Vernon L.	Minneapolis
‡	Lindberg, Winston R.	Minneapolis
‡	Lindblom, Maurice L.	Minneapolis
‡	Lindeland, Arthur T.	Minneapolis
‡	Lindemann, Charles E.	Minneapolis
‡	Linderholm, Bruce E.	Minneapolis
‡	Lindgren, Russell C.	Minneapolis
‡	Lindquist, Richard H.	Minneaoplis
	Lindseth, Esten O.	Minneapolis
*‡	Linner, Gunnar	Minneapolis
‡	Linner, John H.	Minneapolis
‡	Linner, Paul W.	Minneapolis
	Lipschultz, Oscar	Minneapolis
	Litman, Abraham B.	Minneapolis
‡	Litman, Thomas	Minneapolis
†	Lloyd, Judson F.	Minneapolis
	Lober, Paul H.	Minneapolis
	Locke, Murray S.	Minneapolis
‡	Lofsness, Stanley V.	Minneapolis
†‡	Logefeil, Rudolph C.	Minneapolis
‡	Logothetis, John A.	Minneapolis
	Loken, Merle K.	Minneapolis
‡	Lott, Frederick H.	Minneapolis
†	Lovett, Beatrice R.	Minneapolis
	Lowe, Douglass A.	Minneapolis
	Lowry, Elizabeth C.	Minneapolis
	Lowry, Jeanette K.	Minneapolis
	Lowry, Paul T.	Minneapolis
	Lowry, Thomas	Minneapolis
	Lueck, Wallace W.	Minneapolis
‡	Lufkin, Nathaniel H.	Minneapolis
‡	Luh, Edwin F.	St. Paul
	Lund, George W.	Minneapolis
	Lund, Nancy R.	Minneapolis
‡	Lund, Richard R.	Minneapolis
†	Lundberg, Ruth I.	St. Paul
†	Lundblad, Roy A.	Minneapolis
	Lundblad, Stanley W.	Minneapolis
†‡	Lundeberg, Karl R.	Minneapolis
‡	Lundquist, Virgil J. P.	Minneapolis
*†	Lynch, Matthew J.	Minneapolis
	Lynch, Michael F.	Minneapolis
‡	Lynn, Walter	Minneapolis

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	Lyon, Fred A.	Minneapolis
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†‡	Lysne, Henry	Minneapolis
*‡	Lysne, Myron	Minneapolis
#	Lysne, Richard B.	Minneapolis
	Lysyj, Anatol	Minneapolis
‡	Lyzenga, Anton G.	Minneapolis
	McCaffrey, F. John	Minneapolis
‡	McCampbell, Malcolm	Minneapolis
‡	McCannel, Malcolm A.	Minneapolis
‡	McCarthy, Donald	Minneapolis
‡	McCormick, Donald P.	Minneapolis
†	McDaniel, Orianna	Minneapolis
‡	McFarland, Arthur H.	Minneapolis
‡	McGandy, Robert F.	Minneapolis
†	McGeary, George E.	North Ft. Myers, Fla.
‡	McInerny, Maurice W.	Minneapolis
	McKelvey, John L.	Minneapolis
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‡	McKinlay, Gordon L.	Minneapolis
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	Mandel, Sheldon L.	Minneapolis
	Manick, Kenneth P.	Minneapolis
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	Mann, George A.	Minneapolis
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‡	Mark, Aaron L.	Minneapolis
	Mark, Merle S.	Minneapolis
‡	Marking, George H.	Minneapolis
	Markland, Colin	Minneapolis
	Markovitz, Jack M.	Minneapolis
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‡	Martin, George R.	Minneapolis
	Martinson, Carl J.	Wayzata
	Martinson, Elmer J.	Wayzata
‡	Maslansky, Robert A.	Minneapolis
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	Maunder, John B.	Minneapolis
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‡	Maxeiner, S. R., Jr.	Minneapolis
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	Meany, Thomas J.	Minneapolis
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‡	Mensheha, Nicholas M.	Minneapolis
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	Messenheimer, Myron G.	Minneapolis
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†	Meyer, E. Lawrence	Winona
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‡	Michelson, Henry E.	Minneapolis
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	Middlebrook, John E.	Minneapolis
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‡	Miller, Hugo E.	Minneapolis
‡	Miller, J. Carleton	Minneapolis
‡	Miller, William P.	Minneapolis
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	Minsky, Armen A.	Minneapolis
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‡	Mitchell, Edward C.	Mound
‡	Mitchell, Mancel	Minneapolis
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	Moe, W. Wyatt	Minneapolis
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	Moen, Johannes K.	Minneapolis
	Mollers, Theodore P.	Ft. Snelling
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‡	Moore, Irvin H.	Hopkins
	Moorhead, Marie	Minneapolis
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	Moral, Harvey M.	Minneapolis
‡	Moran, Leo J.	New Brighton
	Moriarty, James A.	Minneapolis
	Moriarty, Joseph D.	Coon Rapids
‡	Mork, A. Harold	Anoka
‡	Mork, Frank E.	Anoka
‡	Mork, Frank E., Jr.	Minneapolis
	Morrison, Charlotte J.	Minneapolis
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‡	Moyer, Leonard B.	Minneapolis
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	Mullin, Gerald T.	Minneapolis
	Mulvahill, John E.	Minneapolis
	Munkittrick, Ronald C.	Minneapolis
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	Murray, Elisabeth M.	Minneapolis
	Muske, Marvin M.	Minneapolis
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‡	Nagobads, Ilgvars J.	So. St. Paul
	Nagobads, V. George	Minneapolis
	Nash, Eldore B.	Minneapolis
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†	Nelson, Bernice A.	Minneapolis
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‡	Nesset, Lawren B.	Minneapolis
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	Norval, Mildred A.	St. Paul
	Nuessle, William F.	St. Louis Park
	Nydahl, Bruce C.	Minneapolis
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	O'Brien, Bruce J.	Minneapolis
‡	O'Brien, William A.	Minneapolis
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	Overby, Philip G.	Minneapolis
	Owen, Richard R.	Minneapolis
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	Page, Raymond L.	Minneapolis
	Paisner, Hyman M.	Minneapolis
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	Papermaster, Theodore C.	Minneapolis
	Park, Wilford E.	Minneapolis
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	Perlman, Herschel L.	Minneapolis
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	Petersen, Byron D.	Minneapolis
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	Peterson, W. Henry	Minneapolis
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†‡	Petit, Leon J.	Minneapolis
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‡	Pfohl, Richard A.	Minneapolis
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	Phelps, Robert D.	Minneapolis
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	Pincus, Mitchell	Minneapolis
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‡	Plass, Herbert F. R.	Minneapolis
‡	Pleissner, Karl W.	Minneapolis
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	Pohl, John F.	Minneapolis
	Polesky, Herbert F.	Minneapolis
	Poley, Brooks J.	Minneapolis
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‡	Pollock, Anthony J.	Minneapolis
‡	Polzak, Jacob A.	Minneapolis
	Pone, John J.	Minneapolis
‡	Popadiuk, Peter	Minneapolis
#‡	Popowich, John G.	Minneapolis
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‡	Potter, Robert B.	Minneapolis
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‡	Pratt, Fred J., Jr.	Minneapolis
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	Prickman, William E.	Minneapolis
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	Raab, David E.	Minneapolis
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	Raich, John J.	Minneapolis
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	Randall, David A.	Minneapolis
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	Reed, Sheldon C.	Minneapolis
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‡	Reiser, Milton P.	Minneapolis
‡	Remole, William D.	Minneapolis
‡	Resch, Joseph A.	Minneapolis
	Reynolds, Donald P.	Minneapolis
	Rholl, Arnold O.	Minneapolis
‡	Rice, Carl O.	Minneapolis
	Rice, Fred A.	Minneapolis
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†‡	Richdorf, Lawrence F.	Minneapolis
‡	Rieke, W. W.	Wayzata
	Riley, William J.	Minneapolis
	Riordan, Elsie M.	Minneapolis
‡	Ripple, Rudolph J., Jr.	Minneapolis
‡	Risch, Ronald E.	Minneapolis
‡	Rizer, Dean K.	Minneapolis
†	Robb, Edwin F.	Boca Raton, Florida
‡	Robbins, Owen F.	Minneapolis
‡	Roberts, Byron H.	Minneapolis
‡	Roberts, Lewis J.	Minneapolis
‡	Roberts, Stanley W.	Minneapolis
	Robinson, Cortland O.	Minneapolis
‡	Rock, William H.	Anoka
‡	Rocknem, Robert E.	Minneapolis
	Rockwell, Curtiss V.	Minneapolis
‡	Rodgers, Richard S.	Minneapolis
‡	Rogin, Norton	Minneapolis
‡	Rollins, Pat	Minnetonka
‡	Romness, Kenneth B.	Mound
‡	Rosenbaum, David L.	Minneapolis
	Rosendahl, Frederick G.	Minneapolis
‡	Rosenfield, Abraham B.	Minneapolis
‡	Rosenow, John H.	Minneapolis
†‡	Rosenwald, Reuben M.	Minneapolis
‡	Rossen, Ralph	Minneapolis
	Rotenberg, Robert J.	Minneapolis
	Rotenberg, Samuel	Huntington Park, Calif.
‡	Rothnem, Morris S.	Minneapolis
	Rucker, Thomas K.	Minneapolis
	Rucker, William H.	Minneapolis
†	Rud, Norman E.	Bloomington
	Runquist, Richard K.	Cambridge
‡	Russeth, Arthur N.	Minneapolis
‡	Rusten, Elmer M.	Minneapolis
	Ryan, Patty J.	Minneapolis
	Rydberg, John S.	Minneapolis
	Rydburg, Wayne C.	Minneapolis
‡	Rydland, Arne D.	Minneapolis
‡	St. Cyr, Harry M.	Robbinsdale
‡	St. Cyr, Kenneth J.	Minneapolis
	Salchert, John	Minneapolis
‡	Saliterman, Bernard I.	Minneapolis
	Salmon, Peter A.	Minneapolis
‡	Salovich, Edward L.	Minneapolis
	Salovich, Elmer R.	Minneapolis
‡	Sanchez, Jose S.	Minneapolis
‡	Sandt, Karl E.	Minneapolis
‡	Sanfilippo, Sylvester J.	Minneapolis
	Sartor, Richard	Minneapolis
‡	Sborov, Abe M.	Minneapolis
	Scallen, Raymond W.	Minneapolis
	Scanlan, Patrick J.	Minneapolis
	Schaar, Frances E.	Minneapolis
	Schaefer, Wesley G.	Minneapolis
	Schaffhausen, Irwin F.	Minneapolis
	Schaffhausen, Mildred	Minneapolis
†	Scheldrup, N. H.	Minneapolis
‡	Scherer, L. Raymond	Minneapolis
	Scherling, Sidney S.	Minneapolis
	Schiele, Burtrum C.	Minneapolis
‡	Schissel, Gregory A.	Minneapolis
‡	Schmidt, W. Robert	Minneapolis
†	Schmitt, Samuel C.	Fallbrook, Calif.
	Schneck, Jack I.	Minneapolis
	Schoening, Herbert A.	Minneapolis
	Schoenwetter, William F.	Minneapolis
‡	Schottler, Max E.	Minneapolis
‡	Schrader, Wayne H.	Minneapolis
‡	Schroeder, Albert J.	Minneapolis
‡	Schultz, Alvin L.	Minneapolis
	Schultz, Earl A.	Minneapolis
‡	Schultz, J. Harold	Minneapolis
‡	Schultz, Peter J.	Minneapolis
‡	Schulze, William M.	Minneapolis
‡	Schumacher, John W.	Minneapolis
‡	Schwartz, E. Robert	Minneapolis
†‡	Schwartz, Virgil J.	Minneapolis
‡	Scott, Horace G.	Minneapolis
	Scott, Robert H.	Minneapolis
†	Seaberg, John A.	Pequot Lakes
‡	Seay, James E., III	Minneapolis
	Segal, Edward L.	Minneapolis
‡	Segal, Martin A.	Minneapolis
†	Seham, Max	St. Paul
	Seibel, David I.	Minneapolis
	Seifert, Gregory L.	Excelsior
‡	Seifert, Milton H.	Excelsior
‡	Seifert, Milton H., Jr.	Excelsior
	Semba, Thomas	Minneapolis
‡	Semsch, Robert D.	Wayzata
	Severseike, Odean M.	Minneapolis
‡	Shandorf, James F.	Minneapolis
	Shaperman, Eva P.	Long Lake
‡	Shapiro, Irving	Minneapolis
‡	Shapiro, Sidney K.	Minneapolis
	Shapiro, Stanley W.	Minneapolis
‡	Shattuck, Clark A.	Minneapolis
‡	Shaw, Howard A.	Minneapolis
‡	Shea, Andrew W	Minneapolis
‡	Sher, Lewis	Minneapolis
‡	Sherman, Lloyd F:	Minneapolis
‡	Sherman, Morris H.	Minneapolis
†	Shillington, Maurice A.	Fort Lauderdale, Florida
	Sholler, Lawrence J.	Minneapolis
‡	Shragg, Robert I.	Minneapolis
‡	Shronts, John F.	Minneapolis
‡	Sidell, Franklin D.	Minneapolis
	Siegmann, William C.	Minneapolis
	Sigel, Melvin E.	Minneapolis
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	Silver, John D.	Minneapolis
‡	Simmons, Richard K.	Minneapolis
*†	Simons, Jalmar H.	Minneapolis
‡	Simonson, Donald B.	Minneapolis
†	Simpson, Ellery De W.	Phoenix, Arizona
‡	Sinykin, Melvin B.	Minneapolis
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	Sisterman, Thomas J.	Minneapolis
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	Slosser, Gaius J.	Minneapolis
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*	Smith, Norvin R.	Hastings
‡	Smith, Theodore S.	Minneapolis
‡	Soderlind, Ragnar T.	Minneapolis
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‡	Solhaug, Samuel B.	Minneapolis
‡	Solvason, Harold M.	Minneapolis
	Spain, W. Thomas	Evansville, Indiana
‡	Spano, Joseph P.	Minneapolis
‡	Spencer, Bernard J.	Minneapolis
‡	Spencer, David L.	Anoka
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‡	Sponsel, Kenath H.	Minneapolis
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†	Stanley, Court R.	Minneapolis
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†	Stenstrom, Annette T.	Holmes Beach, Florida
	Stenzel, Donald A.	Minneapolis
	Stenzel, Joseph A.	Minneapolis
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	Sterns, Laurence	Minneapolis
	Sterrie, Norman A.	Minneapolis
‡	Stewart, Marvin J.	Minneapolis
‡	Stiegler, Farrell S.	Minneapolis
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#	Stolee, Curtis N.	Ft. Dauphin, Madagascar
†	Stolee, Thomas A.	Minneapolis
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	Stone, Stanley P.	Minneapolis
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	Stroebel, Jack L.	Minneapolis
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	Strunk, Clarence A.	Minneapolis
	Student, Richard E.	Minneapolis
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‡	Sweetser, Horatio B.	Minneapolis
‡	Sweetser, Theodore H.	Minneapolis
‡	Sweetser, Theodore H., Jr.	Minneapolis
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‡	Swendseen, Carl J.	Minneapolis
	Swenson, Floyd J.	Minneapolis
	Swenson, Richard W.	Minneapolis
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	Symchych, Boris E.	Minneapolis
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	Tambornino, Joseph M.	Minneapolis
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‡	Tangen, George V.	Minneapolis
†	Taylor, Joseph H.	Ft. Lauderdale, Fla.
‡	Taylor, William E.	Minneapolis
	Tchou, Mien-Fa	Minneapolis
	Teal, Peter V.	Minneapolis
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‡	Teynor, Joseph W.	Minneapolis
	Thelemann, Arthur R., Jr.	Minneapolis
	Theobalt, Inge M.	Minneapolis
‡	Thomas, William H.	Long Lake
	Thomes, A. Boyd	Minneapolis
	Thompson, Arthur	Minneapolis
†‡	Thompson, Willis H.	Minneapolis
	Thorsen, David S.	Minneapolis
‡	Thorson, Stuart V.	Minneapolis
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‡	Titrud, Leonard A.	Minneapolis
	Tobin, John A.	Minneapolis
	Tobin, John D.	Minneapolis
	Torres, Fernando	Minneapolis
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	Trach, Benedict B.	Minneapolis
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	Trow, William H.	Hopkins
	Trucker, Earl B.	Minneapolis
	Tsai, Shih Hao	Minneapolis
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	Turkbas, Nejat	St. Paul
‡	Twidwell, Joseph E.	Minneapolis
*	Twomey, John E.	Minneapolis
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	Vaaler, Robert T.	Minneapolis
‡	Valgemae, Romil	Minneapolis
†	Van Nostrand, David M.	Minneapolis
	Veinbergs, Arnolds	Minneapolis
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	Vennes, Jack A.	Minneapolis
	Vik, A. Elliott	Minneapolis
‡	Von Drashek, Stanley C.	Minneapolis
	Vroman, Donald C.	Minneapolis
	Wagner, Christian	Minneapolis
‡	Wagner, Robert M.	Minneapolis
*‡	Wahlquist, Harold F.	Minneapolis
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‡	Waldron, John F.	Minneapolis
‡	Wall, Carl R.	Minneapolis
	Wallinga, Jack V.	Minneapolis
‡	Walonick, Albert L.	Minneapolis
	Walsh, Francis M.	Minneapolis
	Walsh, John G.	Minneapolis
	Walsh, William T.	Minneapolis
	Wang, Yang	Minneapolis
‡	Wangensteen, Owen H.	Minneapolis
	Warren, John W.	Minneapolis
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	Watson, Cecil J.	Minneapolis
	Wattenberg, Lee W.	Minneapolis
	Weatherhead, Donald S. P.	Minneapolis
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‡	Webber, Richard J.	St. Louis Park
‡	Weber, Lowell W.	Minneapolis
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‡	Weiss, Leo	Minneapolis
‡	Wendland, John P.	Minneapolis

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Hennepin County Medical Society (Continued)

	Werner, George	Minneapolis
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†	West, Catherine C.	Edina
‡	Westgate, Hugh D.	Minneapolis
	Wetherby, Macnider	Minneapolis
	Wetherby, Macnider, Jr.	Minneapolis
	Wethington, Joseph F.	Coon Rapids
‡	Wett, Richard J.	Minneapolis
	Wexler, Harold M.	Minneapolis
‡	Wheeler, Robert W.	Minneapolis
	Whitacre, John C., II	St. Louis, Mo.
	White, Asher A.	Minneapolis
†	White, S. Marx	Minneapolis
†	White, Willard D.	Minneapolis
‡	Whitesell, Lloyd A.	Minneapolis
‡	Widen, Wilford F.	Minneapolis
	Wigdahl, Luther O.	Minneapolis
‡	Wilcox, William A.	Minneapolis
	Wild, John J.	Minneapolis
†	Wilder, Kenneth W.	Minneapolis
†	Wilder, Robert L.	Minneapolis
†	Wilder, Russell M., Jr.	Topeka, Kansas
‡	Wilder, Walter L.	Minneapolis
‡	Wilken, Paul A.	Minneapolis
‡	Williams, Henry L.	Minneapolis
‡	Williams, Paul A.	Minneapolis
‡	Williams, Richard E.	Robbinsdale
	Willis, Harper F., Jr.	Minneapolis
‡	Wilson, Robert E.	Minneapolis
‡	Wilson, Thomas M., Jr.	Minneapolis
	Winchell, Paul	Minneapolis
†	Winther, Nora M. C.	Columbus, Ohio
‡	Wippermann, Frederic F.	Minneapolis
‡	Wisiol, Erich S.	Minneapolis
	Wisness, Osmund A.	Minneapolis
	Woellner, Richard C.	Minneapolis
†‡	Wohlrabe, Arthur A.	Minneapolis
‡	Wohlrabe, A. Cabot	Minneapolis
‡	Wohlrabe, Robert G.	Minneapolis
	Wolf, Alfred H.	Ft. Lauderdale, Fla.
‡	Wolter, Frederick H.	Minneapolis
	Woodley, Donald W.	Minneapolis
	Worrell, Philip J.	Minneapolis
‡	Woyda, William C.	Minneapolis
	Wright, Donald L.	Minneapolis
	Wright, Francis S.	Minneapolis
‡	Wright, Thomas D.	Minneapolis
‡	Wright, William S.	Edina
‡	Wuest, Frederick C.	Minneapolis
†	Wynne, Herbert M. N.	Minneapolis
	Yeager, Terrell F.	Anoka
‡	Yelle, Matthew D.	Anoka
‡	Ylvisaker, Ragnvald S.	Minneapolis
	Yonehiro, Earl G.	Minneapolis
	Young, Ronald C.	Minneapolis
	Yue, Wen Y.	Excelsior
	Zahrendt, O. Lewis	Minneapolis
‡	Zarling, V. Richard	Minneapolis
‡	Zaworski, Leo A.	Minneapolis
	Zelickson, Alvin S.	Minneapolis
	Zierold, Arthur A.	Minneapolis
‡	Zinn, Charles W.	Wayzata
‡	Zinter, Ferdinand A.	Minneapolis

KANDIYOHI-SWIFT-MEEKER COUNTY MEDICAL SOCIETY

Kandiyohi, Swift and Meeker Counties
Regular meetings Third Thursday of each month
Annual meeting in November
Number of members 58

PRESIDENT
Michels, Roger P. .... Willmar
SECRETARY
Smith, Lloyd A. .... Willmar

‡	Allison, David D.	Litchfield
†	Anderson, Richard E.	Willmar
	Bloom, Charles H.	Willmar
‡	Bosland, Howard G.	Willmar
	Chunn, Stanley S.	Willmar
	Danielson, Lennox	Litchfield
‡	Dille, Donald E.	Litchfield
‡	Docksey, John W.	Willmar
‡	Dunstan, Paul L.	Willmar
	Eberley, Tobe S.	Benson
	Eichelberger, Dale L.	Willmar
‡	Ellinger, Albert J.	Willmar
	Fedor, Robert D.	Litchfield
†	Frederickson, Alice C.	Willmar
	Gaebe, Milton B.	Clara City
†	Giere, Silas W.	Benson
‡	Gilman, Lloyd C.	Willmar
	Griffin, Richard P.	Benson
‡	Guy, Jack A.	New London
	Hazen, Richard W.	Willmar
‡	Hinderaker, Harris P.	Willmar
‡	Hinz, Walter E.	Willmar
‡	Hodapp, Robert V.	Willmar
	Holm, Donald F.	Minneapolis
	Houts, Joseph C.	Dassel
	Jacobs, Douglas L.	Willmar
	Johnson, Daniel A.	Litchfield
‡	Johnson, Marvin W.	Dassel
‡	Kaufman, Edward J.	Appleton
	Kvale, James N.	Atwater
	Larrabee, Walter F., Jr.	Willmar
	Leitch, Cecil M.	Litchfield
	McCarthy, Austin M.	Willmar
	Macklin, William E.	Litchfield
‡	Meinert, John K.	Willmar
‡	Michels, Roger P.	Willmar
‡	Munneke, Lyle	Clara City
‡	Nelson, Robert H.	Wake Island
	Nolen, William A.	Litchfield
‡	Olson, Gregory M.	Litchfield
‡	Opsahl, Lawrence	Willmar
	Petersen, Donald H.	Willmar
‡	Peterson, Willard E.	Willmar
†	Porter, Oliver M.	Minneapolis
‡	Proeschel, Ray K.	Willmar
#‡	Robinson, William W.	Agana, Guam
‡	Rorem, Joseph A.	Appleton
‡	Ruchie, Warren H.	Willmar
‡	Ruhe, Albert	Willmar
	Rygh, Harold N.	Atwater
	Schnell, Frederick S.	Litchfield
	Skaife, William F.	Benson
‡	Smith, Lloyd A.	Willmar
†‡	Solsem, Frederick N. S.	Spicer
‡	Thompson, Russell A.	Willmar
‡	Wagner, Norman W.	Benson
	Wilmot, Cecil A.	Litchfield
	Wilmot, Harold E.	Litchfield

LYON-LINCOLN COUNTY MEDICAL SOCIETY

Lyon and Lincoln Counties
Regular meetings, 6 meetings Spring and Fall
Annual meeting fourth Tuesday in October
Number of members 24

PRESIDENT
Sutherland, John E. .... Marshall
SECRETARY
Boyum, Allan J. .... Marshall

‡	Boyum, Alan J.	Marshall
‡	Eckdale, John E.	Marshall
‡	Ferguson, William C.	Walnut Grove
‡	Ford, Burton C.	Marshall
‡	Hedenstrom, Philip C.	Marshall
†	Hoidale, Andrew D.	Tracy
	Johnson, C. Percy	Tyler
†	Kreuzer, Titus C.	Fort Snelling
‡	Lee, Norman J.	Tracy
‡	Monson, Leonard J.	Canby
‡	Mueller, LeRoy E.	Hendricks
‡	Muesing, Mark A.	Tyler
‡	Murphy, Joseph E.	Marshall
‡	Myers, John W.	Canby
‡	Olson, Robert T.	Canby
‡	Peterson, Kenneth A.	Marshall
*	Remsberg, Robert R.	Tracy
†	Rohrer, Christian A.	Madison Lake
‡	Sutherland, John E.	Marshall
‡	Taintor, Ronald W.	Marshall
†	Thill, Leonard J.	Traverse City, Mich.
‡	Thompson, Carl O.	Hendricks
†	Vadheim, Alfred L.	Brookings, South Dakota
†	Workman, Warner G.	Tracy
†	Yaeger, Wilbert W.	Excelsior

MC LEOD COUNTY MEDICAL SOCIETY

McLeod County
Regular meetings, third Thursday of each month
Annual meeting, third Thursday in November
Number of members 23

PRESIDENT
Griebie, Grant L. .... Brownton
SECRETARY
Smyth, John J. .... Lester Prairie

‡	Blackwell, Leonard H.	Hutchinson
‡	Bretzke, Carl O.	Hutchinson
	Carroll, John J.	Winsted
‡	Chervenak, William A.	Minneapolis
‡	Dysterheft, Adolf F.	Gaylord
‡	Griebie, Grant L.	Brownton
‡	Huebert, Dan W.	Hutchinson
‡	Jensen, Alvin M.	Brownton
#‡	Kapsner, Adrian L.	Ogallala, Nebraska
	Knoche, Harvey A.	Gaylord
‡	Lippmann, Elmer W.	Hutchinson
‡	McCoy, Donald E.	Glencoe
‡	McNeil, Maurice R.	Glencoe
‡	Navratil, Donald R.	Glencoe
‡	Neumaier, Arthur	Glencoe
‡	Ohmann, Ronald	Glencoe
‡	Peterson, Kenneth H.	Hutchinson
‡	Schroeppel, John E.	Winthrop
‡	Selmo, Joseph D.	Norwood
‡	Smith, George R.	Hutchinson
‡	Smyth, John J.	Lester Prairie
	Stifter, A. J.	Winsted
‡	Truesdale, Clark W.	Glencoe

MOWER COUNTY MEDICAL SOCIETY

Mower County
Regular meetings, last Friday of the month
Annual meeting, November
Number of members 39

PRESIDENT
Muchow, Gene C. .... Austin
SECRETARY
Todd, John C. .... Austin

‡	Anderson, David P., Jr.	Austin
‡	Anderson, Harold J.	Austin
‡	Barber, Tracy E.	Austin
‡	Christian, William L.	Austin
‡	Cronwell, Bernhard J.	Austin
	Elliott, Harold J.	Hayfield
‡	Hagen, John D.	Austin
†	Havens, John G. W.	Minneapolis
†	Hertel, Garfield E.	McAllen, Texas
‡	Hesla, Inman A.	Austin
‡	Isele, Reginald H.	Austin
†	Leck, Paul C.	Palm Desert, Calif.
‡	Lommen, Morris L.	Austin
†‡	Lommen, Peter A.	Austin
‡	Lommen, Peter A., Jr.	Austin
†	McKenna, Jay K.	LaJolla, California
‡	Mathers, John E.	Austin
‡	Miller, Herman	Austin
‡	Mlinar, Joseph P.	Austin
†	Morse, Morton P.	LeRoy
	Morse, Roger D.	LeRoy
‡	Muchow, Gene C.	Austin
‡	Nesse, James A.	Austin
‡	O'Rourke, William J.	Austin
‡	Patten, John C.	Austin
†	Paulus, Harold E.	Santa Monica, Calif.
	Pesonen, Clifford A.	Austin
‡	Peterson, Stanley C.	Austin
‡	Roberts, George A.	Austin
†	Robertson, Paul A.	Austin
‡	Rosenthal, F. Harold	Austin
‡	Seery, Thomas M.	Austin
†	Smythe, Gwendolyn	Austin
‡	Smythe, Lowell J.	Austin
‡	Stahl, George W.	Austin
‡	Taufic, Mansur	Austin
‡	Todd, John C.	Austin
	Twiggs, Leo F.	Austin
‡	Van Cleve, Horatio P., Jr.	Austin
‡	Wright, Robert R.	Austin

NICOLLET-LE SUEUR COUNTY MEDICAL SOCIETY

Nicollet and LeSueur Counties
Regular meetings, first Monday of even months
Annual meeting, December
Number of Members 27

	PRESIDENT	
	Olmanson, M. Donald	St. Peter
	SECRETARY	
	Anderson, Jo E.	LeSueur
‡	Anderson, Jo E.	LeSueur
†	Branham, Donald S.	Deer Park, Wis.
	Brink, Donald	St. Peter
‡	Curtis, Rauen A.	Le Center
‡	Engstrom, George E.	St. Peter
†	Ericson, Swan	Los Angeles, California
	Gislason, Solveig T.	St. Peter
‡	Greene, Gordon	Arlington
‡	Grimes, Burton P.	St. Peter
	Haes, Julius E.	St. Peter
‡	Hiniker, Peter J.	St. Peter
†	Kabrick, Ola A.	Hull, Illinois
	Kath, Reinhard H.	Arlington
	Larson, Milo H.	St. Peter
‡	Lenander, Mellvin E. L.	St. Peter
	Ninneman, Newton N.	St. Peter
‡	Olmanson, Edmund G.	St. Peter
	Olmanson, M. Donald	St. Peter
‡	Olmanson, Vern	St. Peter
	Sauer, Jean C.	St. Peter
	Sheppard, Charles G.	St. Peter
‡	Sjostrom, Lawrence E.	St. Peter
‡	Sonnesyn, Nels N.	LeSueur
‡	Strathern, Carleton S.	St. Peter
	Thompson, A. Henry	St. Peter
	Vener, John M.	Arlington
‡	Walden, Archie D.	LeSueur
	Wohlrabe, Clarence F.	North Mankato

PARK REGION DISTRICT AND COUNTY MEDICAL SOCIETY

Douglas, Grant, Otter Tail & Wilkin Counties
Regular meetings, March, June, September and December
Annual meeting, December
Number of members 68

	PRESIDENT	
	Estrem, Ralph L.	Fergus Falls
	SECRETARY	
	Sethre, Arthur E.	Fergus Falls
†	Arndt, Harry W.	Detroit Lakes
	Asp, Donald	Milaca
	Baker, Jeannette L.	Fergus Falls
	Baker, Norman H.	Fergus Falls
‡	Bateman, Clarence V.	Fergus Falls
‡	Boline, Clifford A.	Battle Lake
‡	Cain, James H.	Alexandria
‡	Campbell, Denis V.	Fergus Falls
‡	Carlson, Carl E.	Alexandria
	Carlson, Homer J.	Pelican Rapids
‡	Clifford, George W.	Alexandria
‡	Colman, Edward L.	Fergus Falls
‡	Daehlin, Rolf	Fergus Falls
	Doms, Vernon A.	Elbow Lake
‡	Eddy, Richard L.	Alexandria
‡	Emerson, Edwin E.	Osakis
‡	Estrem, Ralph L.	Fergus Falls
‡	Estrem, Robert D.	Fergus Falls
‡	Geiser, Peter M.	Alexandria
‡	Hanson, Everett C.	New York Mills
‡	Heegaard, William G.	Alexandria
‡	Helseth, Hovald K.	Fergus Falls
†	Hildebrand, L. D.	Minneapolis
‡	Hom, Leong Y. W.	Battle Lake
‡	Jacobson, Clifford W.	Breckenridge
‡	Johnson, Arthur G., Jr.	Fergus Falls
‡	Kevern, Jay L.	Henning
‡	Kippen, Neil	Breckenridge
‡	Korda, Henry A.	Pelican Rapids
‡	Kuhlmann, Vernon G.	Alexandria
	Larson, Dorette W.	Fergus Falls
‡	Lewis, Charles W.	Henning
†	Love, Frederick A.	Carlos
	Lu, Cheng-en	Fergus Falls
‡	Lund, Carl J. T.	Fergus Falls
†	Mortensen, Nels G.	Minneapolis
‡	Mouritsen, Glenn J.	Fergus Falls
†‡	Nakamura, James Y.	Excelsior
‡	Nelson Roy A.	Fergus Falls
‡	Ness, Richard A.	Fergus Falls
‡	Nicholson, Richard W.	Fergus Falls
‡	O'Brien, Louis T.	Breckenridge
	Olson, Frances P.	Fergus Falls
‡	Orandi, Mehdi	Fergus Falls
	Ostergaard, Erling	Elbow Lake
†	Parson, Lester R.	Elbow Lake
†	Patterson, William L.	Fergus Falls
	Pawlyszyn, Julian	Fergus Falls
‡	Perkins, Douglass E.	Alexandria
‡	Reinhardt, James H.	Alexandria
‡	Richter, Paul H.	Fergus Falls
‡	Rockwood, Philo H.	Fergus Falls
‡	Sanderson, David J.	Fergus Falls
†	Sather, Edgar R.	Alexandria
	Schamber, Walter E.	Parkers Prairie
	Schoeneberger, P. B.	Perham
‡	Sethre, Arthur F.	Fergus Falls
‡	Shaver, Ward	Fergus Falls
	Singbeil, J. H.	Breckenridge
	Sporre, Knute A.	Fergus Falls
‡	Stahn, Louis H.	Fergus Falls
‡	Stemsrud, Harold L.	Alexandria
‡	Syverson, Leslie A.	Fergus Falls
‡	Tanquist, Edwin J.	Alexandria
‡	Tanquist, Edwin J., Jr.	Alexandria
	Warner, James J.	Perham
‡	Wasson, Loren F.	Alexandria
‡	Webb, Alexander G.	Elbow Lake

RAMSEY COUNTY MEDICAL SOCIETY

Ramsey County
Regular meetings, last Monday each month except June, July & August
Annual meeting in January
Number of members 554

	PRESIDENT	
	McGroarty, Brian J.	St. Paul
	SECRETARY	
	Hollinshead, William H.	St. Paul
	SEC'Y-EXECUTIVE OFFICE	
	Olson, Mrs. Eleanor	St. Paul
‡	Abrams, Alexander, Jr.	St. Paul
‡	Adair, Albert F., Jr.	St. Paul
	Adams, Harold R.	St. Paul
‡	Ahrens, Robert M.	St. Paul
‡	Albrecht, Raymond J.	St. Paul
‡	Alden, John F.	St. Paul
‡	Alton, Donald G.	St. Paul
‡	Amerongen, Werner W.	St. Paul
	Anderson, James J.	St. Paul
	Anderson, Margaret C.	St. Paul
‡	Anderson, Richard W.	St. Paul
‡	Arny, Frederick P.	St. Paul
‡	Arzt, Philip K.	St. Paul
	Ashmore, Herbert C.	St. Paul
‡	Auran, David B.	St. Paul
‡	Aurelius, J. Richards	St. Paul
‡	Ausman, Duane R.	St. Paul
‡	Austrian, Sol	St. Paul
‡	Babb, Frank S.	St. Paul
	Bach, Jerome M.	St. Paul
‡	Bah, Merle C.	St. Paul
	Baker, Chilton R., Jr.	St. Paul
	Balce, Regino V.	St. Paul
	Barnett, Joseph M.	St. Paul
†	Barsness, Nellie O. N.	St. Paul
	Bauer, Eugene L.	St. Paul
‡	Beck, Charles J.	North St. Paul
‡	Beek, Harvey O.	St. Paul
‡	Beer, John J.	St. Paul
‡	Bellomo, James	St. Paul
	Belz, Reinmar	St. Paul
‡	Benepe, James L.	St. Paul
	Benthack, Elaine M.	Minneapolis
	Bernier, M. J.	North St. Paul
‡	Bernstein, William C.	St. Paul
‡	Bicek, Joseph F.	St. Paul
‡	Bjornson, Robert G. B.	Wailuku, Hawaii
	Black, Earl J.	White Bear Lake
	Blackburn, Henry W., Jr.	St. Paul
‡	Blomberg, William R.	St. Paul
‡	Blumberg, Henry B.	St. Paul
†	Bock, Rolland A.	St. Paul
	Boies, Lawrence B., Jr.	St. Paul
‡	Bonello, Frank J.	St. Paul
‡	Borg, Joseph F.	St. Paul
†	Bouma, Lewis R.	St. Paul
‡	Brainard, John B.	St. Paul
†	Bray, Elwyn R.	St. Paul
‡	Briggs, John F.	St. Paul
‡	Briggs, Thomas G.	White Bear Lake
	Broadie, Thomas E.	St. Paul
†‡	Brodie, Walter D.	St. Paul
	Broman, Harold R., Jr.	North St. Paul
	Brown, Charles T.	St. Paul
	Brown, Hector M.	St. Paul
	Brown, James E., Jr.	St. Paul
†	Brown, John M.	Rochester
‡	Bulinski, Theodore J.	St. Paul
‡	Burklund, Edwin C.	St. Paul
‡	Burlingame, David A.	St. Paul
‡	Burmeister, Richard O.	St. Paul
	Burton, J. Richard	St. Paul
‡	Bush, Robert P.	St. Paul
†‡	Busher, Herbert H.	St. Paul
‡	Byrne, William J.	St. Paul
‡	Cain, Clark L.	St. Paul
‡	Canine, James L.	South St. Paul
‡	Carey, Lewis S.	St. Paul
	Cedarleaf, Cherry B.	Middletown, Conn.
†‡	Chatterton, Carl C.	St. Paul
‡	Cich, John A.	St. Paul
	Clark, Henry B., Jr.	Minneapolis
‡	Cochrane, Byron B.	St. Paul
	Coddon, Walter D.	St. Paul
†‡	Colby, Woodard L.	St. Paul
	Cole, Wallace H.	St. Paul
‡	Coleman, John B.	St. Paul
	Colton, Roger S.	St. Paul
‡	Comfort, Thomas H.	St. Paul
‡	Connolly, Coleman J.	St. Paul
	Connolly, Joseph P.	South St. Paul
†	Connor, Charles E.	St. Paul
†‡	Cook, C. Kenneth	St. Paul
	Cooper, Charles C.	Moose Lake
†	Countryman, Roger S.	Saratoga, California
‡	Craig, David M.	St. Paul
	Cram, Barclay M.	St. Paul
	Crowley, James H.	St. Paul
‡	Crudo, Vincent D.	St. Paul
‡	Crum, Arthur Z.	St. Paul
	Crump, James W.	St. Paul
‡	Culligan, John A.	St. Paul
‡	Culver, Lucian G.	St. Paul
‡	Cumming, E. Dale	St. Paul
‡	Davis, Edward V.	St. Paul
	Dawson, James R.	St. Paul
	Decker, Charles H.	St. Paul
†‡	Derauf, Benjamin I.	St. Paul
‡	Derauf, Donald E.	St. Paul
	Derechin, William	St. Paul
‡	Deters, Donald C.	St. Paul
‡	Dinsdale, Howard A.	St. Paul
‡	Dolmage, George H.	St. Paul
‡	Dooley, Robert T.	St. Paul
*‡	Drake, Carl B.	St. Paul
	Dunn, Robert C.	St. Paul
‡	Durkin, John L.	St. Paul
‡	Duvall, Arndt J., III	Minneapolis
‡	Dyrdal, Paul J.	St. Paul
‡	Earl, George A.	St. Paul
‡	Earl, John R.	St. Paul
	Edwards, J. Willard	St. Paul
‡	Edwards, Jesse E.	St. Paul
	Edwards, Lloyd G.	St. Paul
‡	Edwards, Richard B.	St. Paul
‡	Edwards, Thomas J.	St. Paul
‡	Eelkema, Herman H.	St. Paul
	Eginton, Charles T.	St. Paul
	Emerson, Edward C.	St. Paul

Continued on Next Page

Ramsey County Medical Society (Continued)

‡	Emmons, Robert W.	St. Paul
	Endress, Edward K.	St. Paul
	England, Rodney W.	St. Paul
‡	Enroth, Oscar E.	St. Paul
‡	Erlanson, A. Cornell	St. Paul
‡	Ersfeld, Murray P.	St. Paul
	Falk, Abraham	St. Paul
	Farkas, John V.	St. Paul
‡	Fee, John G.	St. Paul
‡	Felder, Davitt A.	St. Paul
‡	Felion, Arthur J.	St. Paul
‡	Ferguson, John N.	St. Paul
‡	Fesler, Harold H.	St. Paul
‡	Fink, Daniel L.	St. Paul
†‡	Fischer, Robert F.	St. Paul
‡	Fisher, Dan W.	St. Paul
‡	Flannery, Hubert F.	St. Paul
	Flom, Reynold P.	St. Paul
‡	Flom, Robert S.	St. Paul
‡	Flynn, Louis L., Jr.	St. Paul
‡	Flynn, Robert A.	St. Paul
†	Fogarty, Charles W.	St. Paul
‡	Fogelberg, Emil J.	St. Paul
*†	Foley, Frederic E. B.	St. Paul
	Forsythe, James R.	St. Paul
‡	Fox, LeRoy J.	St. Paul
‡	Freeman, Charles D., Jr.	St. Paul
	Fritz Wallace L.	St. Paul
‡	Froats, Charles W.	St. Paul
‡	Frye, Charles W.	St. Paul
‡	Fuller, Benjamin F.	St. Paul
	Funke, Joyce L.	St. Paul
‡	Gaertner, Frank M. J., Jr.	St. Paul
‡	Gaertner, John R.	St. Paul
‡	Galligan, John J.	St. Paul
	Galway, Charles F.	St. Paul
‡	Gardner, Walter P.	St. Paul
	Garrow, Douglas M.	St. Paul
	Gaute, Svend T.	St. Paul
†‡	Gehlen, Joseph N.	St. Paul
‡	Geist, Robert W.	St. Paul
	Gibbs, Edward C.	St. Paul
‡	Gilchrist, Milton R.	St. Paul
‡	Gillespie, Delmar R.	St. Paul
‡	Gilsdorf, Donald A.	St. Paul
‡	Gleason, Wallace A.	St. Paul
‡	Glenny, William R.	St. Paul
‡	Goldsmith, Joseph W.	St. Paul
	Goodman, Ernest	St. Paul
‡	Govrik, Kalman	St. Paul
#	Greenough, William G.	Ft. Carson, Colo.
	Gretsch, Gerald A.	St. Paul
‡	Griffin, Patrick J.	St. Paul
	Griffin, Thomas M.	St. Paul
‡	Guenther, Dean E.	West St. Paul
‡	Gumnit, Robert J.	St. Paul
‡	Guthrie, J. Cameron	St. Paul
‡	Hakanson, Erick Y.	St. Paul
‡	Hall, Barnard	St. Paul
‡	Hammarsten, James F.	St. Paul
†‡	Hammes, Ernest M.	St. Paul
‡	Hammes, Ernest M., Jr.	St. Paul
‡	Hannon, Donald W.	St. Paul
‡	Harmon, Gaius E.	St. Paul
‡	Harris, John E.	Minneapolis
‡	Harris, Max E.	St. Paul
‡	Hartfiel, William F.	St. Paul
	Hartig, Marjorie	St. Paul
†‡	Hauser, Victor P.	St. Paul
‡	Hawkinson, Harlan W.	St. Paul
‡	Hayes, Albert F.	St. Paul
‡	Heck, William W.	St. Paul
†	Hedenstrom, Charles W.	St. Paul
	Hedenstrom, Frank G.	St. Paul
‡	Hedenstrom, Richard H.	St. Paul
	Hedlund, Charles J.	St. Paul
	Heilig, William R.	St. Paul
	Henderson, Terrance P.	White Bear Lake
†‡	Hengstler, William H.	St. Paul
‡	Henke, Wilbert J.	St. Paul
‡	Henry, James S.	St. Paul
†	Herman, Samuel M.	St. Paul
	Herrick, Donald W.	St. Paul
‡	Hetzler, John A.	St. Paul
‡	Hilger, Jerome A.	St. Paul
‡	Hilger, John	St. Paul
‡	Hilger, Laurence D.	St. Paul
‡	Hilker, Marcus D.	St. Paul
	Hill, Charlotte W.	St. Paul
	Hiniker, Louis P.	St. Paul
‡	Ho, Shu Kang	St. Paul
*†‡	Hochfilzer, John J.	St. Paul
	Hodgson, Jane E.	St. Paul
‡	Hohmann, Albert	St. Paul
†	Holcomb, O. William	St. Paul
	Hollinshead, William H.	St. Paul
‡	Holmen, Robert W.	St. Paul
†	Holt, John E.	St. Paul
	Hopkins, G. Wendell	Minneapolis
	Houlton, William H.	St. Paul
*†	Howard, Merrill A.	St. Paul
‡	Howe, Newell W.	West St. Paul
	Hughes, Gary W.	St. Paul
	Hunter, Murray H.	Farmington
‡	Hunter, Samuel W.	St. Paul
‡	Hurwitz, Milton M.	St. Paul
‡	Huseby, Thomas L.	St. Paul
‡	Husebye, Kjeld O.	St. Paul
†	Ide, Arthur W.	St. Paul
‡	Jackson, William C.	St. Paul
‡	James, Ellery M.	St. Paul
‡	James, John W.	St. Paul
‡	Janssen, Martin E.	St. Paul
	Jarvis, Bruce W.	Houston, Texas
	Jarvis, Charles W.	St. Paul
‡	Jastram, Rupert M.	St. Paul
‡	Johanson, Waldemar G.	St Paul
	Johnson, Carl E.	St. Paul
	Johnson, Carolyn A.	St. Paul
‡	Johnson, Herbert W.	St. Paul
‡	Johnson, Richard J.	St. Paul
‡	Johnson, Thomas E.	St. Paul
	Joseph, Arnold H.	St. Paul
‡	Kane, Dennis J.	St. Paul
	Kaplan, David H.	Minneapolis
‡	Karon, Everett H.	St. Paul
‡	Karon, Irvine M.	St. Paul
‡	Kasper, Eugene M.	St. Paul
	Katz, Louis J.	Long Beach, California
‡	Kelly, Albert C.	St. Paul
‡	Kelly, Edward H.	St. Paul
	Kelly, Helen M.	St. Paul
‡	Kelly, Joseph R.	St. Paul
‡	Kelsey, Chauncey M.	St. Paul

Ramsey County Medical Society (Continued)

‡	Kenefick, Emmett V.	St. Paul
‡	Kenyon, Thomas J.	St. Paul
†‡	Kesting, Herman	St. Paul
‡	Knutson, Gerhard E.	St. Paul
‡	Knutson, Robert C.	St. Paul
	Kodres, Nina	St. Paul
‡	Kosiak, Michael	St. Paul
	Koza, Donald W.	St. Paul
	Kraatz, Robert W.	St. Paul
‡	Kramer, James D.	St. Paul
‡	Krezowski, Thomas K.	St. Paul
‡	Kugler, Alex A.	St. Paul
‡	Kuske, Albert W.	St. Paul
‡	Kusske, Bradley W.	St. Paul
‡	Kusske, Douglas R.	St. Paul
†‡	Kvam, Lowell	St. Paul
	Lade, Roswith I.	St. Paul
‡	Lane, Miles I.	White Bear Lake
‡	Lannin, Bernard G.	St. Paul
‡	Lannin, Donald R.	St. Paul
	Larson, Eva Jane Ostergren	St. Paul
‡	Laszewski, Franz von Zelberschwecht	St. Paul
‡	Lawler, Kevin M.	St. Paul
	Lees, Jack R.	St. Paul
	Lehman, Donald S.	St. Paul
‡	Leick, Richard M.	St. Paul
†	Leitch, Archibald	St. Paul
‡	Leonard, Stanley A.	St. Paul
†	Lepak, John A.	St. Paul
‡	Lerdahl, Kenneth	St. Paul
‡	Lessard, Richard J.	St. Paul
	Leven, N. Logan	St. Paul
‡	Leverenz, Carleton W.	St. Paul
	Levitt, George X.	St. Paul
‡	Lewis, Glenn M., Jr.	St. Paul
	Lewis, Joyce S., Jr.	St. Paul
‡	Lick, Charles L.	St. Paul
‡	Lick, William J.	St. Paul
‡	Lien, Richard J.	St. Paul
†	Lightbourn, Edgar L.	Hastings
‡	Lilleberg, Norbert J.	St. Paul
‡	Lillie, Andrew R.	St. Paul
‡	Lindell, Robert E.	St. Paul
‡	Lindquist, Max F.	South St. Paul
	Lippman, Hyman S.	St. Paul
	Litkewitsch, Helene	St. Paul
‡	Loken, Selmer M.	St. Paul
	Lowe, Alexander D.	South St. Paul
	Lowe, Thomas A.	South St. Paul
‡	Lundholm, Arthur M.	Harris
‡	Lunzer, Richard G.	St. Paul
‡	Lynch, Francis W.	St. Paul
	Lynch, Richard P.	St. Paul
	Lyne, Benjamin W.	St. Paul
‡	McCain, Donovan L.	St. Paul
	McCarthy, Charles J.	St. Paul
	McClanahan, Thomas S.	White Bear Lake
	McClellan, Robert J.	St. Paul
	McCloud, C. Naumann	St. Paul
‡	McEllistrem, Edward J.	St. Paul
‡	McEllistrem, Gerald D.	St. Paul
‡	McEwan, Alexander	St. Paul
	McGinnis, Edward A.	St. Paul
‡	McGroarty, Brian J.	St. Paul
	McHutchison, Samuel K.	St. Paul
	McKenzie, Eva E.	St. Paul
‡	McNeill, John A.	St. Paul
	MacCornack, Robert L. Jr.	South St. Paul
	Mackoff, Sam M.	Phoenix, Arizona
	Madland, Robert S.	St. Paul
	Magary, Victor J., Jr.	St. Paul
‡	Malerich, J. Anthony	West St. Paul
‡	Manlove, Charles H., Jr.	St. Paul
	Marks, Roger W.	St. Paul
‡	Martin, Dwight L.	St. Paul
†‡	Martineau, Joseph L.	St. Paul
	Mateo, Guillermo	St. Paul
	Matthews, James H.	Minneapolis
‡	Mazzitello, William F.	St. Paul
‡	Mears, Burtis J.	St. Paul
‡	Medelman, John P.	St. Paul
‡	Melancon, Joseph F.	St. Paul
‡	Menold, William F.	St. Paul
‡	Merrick, Robert L.	St. Paul
‡	Michienzi, Leonard J.	St. Paul
‡	Miller, Albert G.	St. Paul
	Miller, Winston R.	St. Paul
	Miller, Zondal R.	St. Paul
‡	Milnar, Frank J.	St. Paul
	Milroy, Thomas W.	Minneapolis
‡	Mishek, Charles J.	St. Paul
‡	Mitchell, George S.	St. Paul
†	Molander, Herbert A.	St. Paul
‡	Monahan, Robert H.	St. Paul
‡	Mooney, Robert D.	St. Paul
*†	Moquin, Marie A.	St. Paul
†	Moren, J. Adelaide	St. Paul
‡	Muchmore, Harold G.	St. Paul
‡	Muller, A. Eugene	North St. Paul
	Mundahl, Harold R.	St. Paul
	Murphy, Jack T.	St. Paul
‡	Murray, Roger C.	St. Paul
‡	Neher, Frederick J.	St. Paul
	Neibergs, Lydia I.	St. Paul
	Neibergs, Paul	St. Paul
‡	Nelson, Loren E.	St. Paul
‡	Nelson, Louis A., Jr.	St. Paul
‡	Nelson, Ronald J.	St. Paul
	Nesvacil, Leon	St. Paul
‡	Nichols, Thomas O.	St. Paul
‡	Nimlos, Kenneth O.	St. Paul
†	Nimlos, Lenore O.	St. Paul
‡	Norman, David D.	St. Paul
	Nuebel, Charles J.	Long Beach, California
†	Nye, Katherine A.	St. Paul
	Nye, Lillian L.	St. Paul
‡	O'Brien, John C.	St. Paul
	O'Kane, Thomas W.	St. Paul
‡	O'Malley, Valentine	St. Paul
	O'Neill, Nial C.	St. Paul
†	O'Reilley, Bernard E.	St. Paul
	Ockuly, Orville E.	St. Paul
†	Ogden, Warner	St. Paul
†	Ohage, Justus	St. Paul
‡	Olsen, Ralph L.	St. Paul
	Olson, Barbara F.	South St. Paul
‡	Osekowsky, Henry J.	St. Paul
†‡	Ostergren, Edward W.	St. Paul
	Ouellette, Alfred J.	St. Paul
‡	Owens, Frederick M.	St. Paul
‡	Palm, Neil M.	St. Paul
‡	Paulson, Elmer C.	St. Paul
‡	Paulson, Wallace J.	St. Paul

Continued on Next Page

Ramsey County Medical Society (Continued)

†	Pearson, Fritz R.	St. Paul
‡	Pearson, Malcolm M.	St. Paul
†	Pedersen, Arthur H.	St. Paul
‡	Perry, John F., Jr.	St. Paul
*	Peterson, David B.	St. Paul
‡	Peterson, Donald H.	St. Paul
‡	Peterson, Edward A.	St. Paul
‡	Peterson, Harold O.	Minneapolis
	Peterson, Joel L. E.	St. Paul
	Peterson, Roy L.	White Bear Lake
	Phillips, John B.	St. Paul
	Phillips, Leonard	St. Paul
‡	Plotke, Harry L.	St. Paul
	Polski, Paul G.	South St. Paul
‡	Post, Edmund A.	St. Paul
‡	Powers, Robert L.	St. Paul
†‡	Prentice, Walter B.	St. Paul
‡	Proud, Harry S.	St. Paul
†	Quattlebaum, Frank W.	St. Paul
‡	Raaen, Olaf J.	St. Paul
	Rabcevich, Anatole	St. Paul
‡	Ralph, James R.	St. Paul
	Ramlow, Ralph M.	St. Paul
†	Ramsey, Walter R.	St. Paul
	Rasmussen, Ramby C.	St. Paul
‡	Raths, Otto N., Jr.	St. Paul
‡	Ravits, Harold G.	St. Paul
‡	Rea, Charles E.	St. Paul
	Redleaf, Paul D.	St. Paul
‡	Reid, James W.	South St. Paul
	Reif, Robert W.	White Bear Lake
	Richards, Albert M.	St. Paul
‡	Richardson, Edward J., Jr.	St. Paul
‡	Rick, Paul F. W.	St. Paul
‡	Rinkey, Eugene	St. Paul
	Ripple, Rudolph J.	St. Paul
‡	Ritchie, Wallace P.	St. Paul
‡	Ritt, Albert E.	St. Paul
‡	Roach, Charles A.	St. Paul
‡	Roach, Donald E.	St. Paul
	Rolig, David H.	St. Paul
‡	Rollie, Orris O.	St. Paul
	Root, Harlan D.	San Antonio, Texas
‡	Rosenthal, Robert	St. Paul
	Rossing, Robert G.	San Antonio, Texas
‡	Roth, George C.	St. Paul
†‡	Rothschild, Harold J.	St. Paul
‡	Rowe, Clarence J., Jr.	St. Paul
‡	Roy, Philemon C.	St. Paul
†	Ruhberg, George N.	Santa Barbara, California
‡	Rukavina, John G.	St. Paul
‡	Rushay, Arthur J.	White Bear Lake
‡	Rusterholz, Alan P.	St. Paul
†‡	Ryan, John J.	St. Paul
‡	Ryan, Joseph M.	St. Paul
	Sand, Richard E.	St. Paul
‡	Sandkamp, Virgil A.	South St. Paul
	Scherek, Jerome J.	St. Paul
‡	Schloff, Ivan	St. Paul
*‡	Schmidt, Herbert W.	St. Paul
	Schmidtke, Reinhardt L.	St. Paul
†	Schoch, Robert B. J.	St. Paul
‡	Schochet, H. Laurence	St. Paul
†‡	Schons, Edward	Minneapolis
	Schossow, George W.	White Bear Lake
‡	Schroeckenstein, Hugo F.	St. Paul
‡	Schuft, James R.	St. Paul

	Schultz, Donald O.	Minneapolis
	Schwyzer, Marquerite	St. Paul
‡	Scott, Eugene E.	St. Paul
	Sekhon, Mohan S.	St. Paul
‡	Sells, Richard J.	St. Paul
‡	Setzer, Hobert J.	St. Paul
	Severson, Donald R.	St. Paul
†	Shannon, William R.	Faribault
‡	Shelander, Marcus I.	St. Paul
†	Shellman, John J.	Pacific Palisades, California
	Short, Marshall H.	St. Paul
‡	Simons, Leander T.	St. Paul
	Siegel, Clarence	St. Paul
‡	Singer, Benjamin J.	St. Paul
‡	Skinner, Abbott	St. Paul
†	Skinner, Harvey O.	St. Paul
‡	Smiley, Donald P.	St. Paul
‡	Smisek, Elmer A.	St. Paul
	Smith, H. Nippert	St. Paul
‡	Smith, Vernon D. E.	St. Paul
‡	Smith, William T.	St. Paul
†‡	Snyder, George W.	St. Paul
†‡	Sohlberg, Olof I.	St. Paul
‡	Sommerdorf, Vernon L.	St. Paul
‡	Sorem, Milton B.	St. Paul
‡	Soucheray, Philip H.	St. Paul
†‡	Souster, Benjamin B.	St. Paul
‡	Sowada, Ernest J.	St. Paul
‡	Sperl, Michael P., Jr.	St. Paul
	Sprafka, Gregory A.	St. Paul
‡	Sprafka, Joseph L.	St. Paul
‡	Spraitz, Anton F, Jr.	St. Paul
	Stafne, John G.	St. Paul
	Stein, Robert L.	North St. Paul
‡	Steinberg, Charles L.	St. Paul
‡	Sterner, Donald C.	St. Paul
‡	Sterner, Ernest R.	St. Paul
‡	Sterner, John J.	St. Paul
	Stolpestad, Armer H.	St. Paul
	Straus, Maurice L.	St. Paul
‡	Strem, Edward L.	St. Paul
	Strickland, Martha J. B.	St. Paul
‡	Sturley, Rodney F.	St. Paul
	Sullivan, W. Albert, Jr.	St. Paul
†	Swanson, John A.	St. Paul
‡	Swanson, Lawrence J.	West St. Paul
‡	Swanson, Ralph H.	West St. Paul
	Swendson, James J.	St. Paul
‡	Swenson, Donald B.	St. Paul
	Tanasichuk, Murray A.	St. Paul
‡	Tani, George	St. Paul
‡	Teeter, Richard R.	St. Paul
‡	Teisberg, John E.	St. Paul
*	Thompson, Floyd A.	St. Paul
‡	Thompson, Wayne W.	St. Paul
	Thoreson, M. C. Bernice	South St. Paul
‡	Tiffany, Francis B.	St. Paul
‡	Tifft, Cyril R.	St. Paul
‡	Tongen, Lyle A.	St. Paul
‡	Travis, James S.	St. Paul
	Tregilgas, Richard B.	St. Paul
	Trotman, Neil M.	St. Paul
	Tveten, Omar A.	St. Paul
‡	Ubel, Frank A.	St. Paul
	Vail, David J.	St. Paul
	Van Bergen, Frederick H.	Minneapolis
	Van De Riet, Lowell W.	St. Paul
	Varco, Richard L.	St. Paul

Ramsey County Medical Society (Continued)

‡	Vaughn, C. Gordon	St. Paul
	Veirs, Dean M.	Hastings
†	Veirs, Ruby J. S.	Hastings
†‡	Venables, Alexander E.	Ely
	Venters, Homer D., Jr.	St. Paul
‡	Votel, Thomas W.	St. Paul
†‡	Waas, Charles W.	St. Paul
‡	Walker, Arthur E.	St. Paul
‡	Wall, James O.	St. Paul
‡	Walsh, Edward F.	St. Paul
‡	Walter, Clarence W.	St. Paul
‡	Warner, Clyde M.	St. Paul
	Warren, Cecil A.	St. Paul
	Waters, Alvin W.	St. Paul
‡	Watson, P. Theodore	St. Paul
‡	Watson, William H. A.	St. Paul
‡	Watson, William J.	Newport
	Watz, Clarence E.	St. Paul
‡	Webber, Fred L.	St. Paul
‡	Wedes, Deno J.	St. Paul
	Wegleitner, Mark J.	West St. Paul
‡	Weis, Benjamin A.	St. Paul
‡	Weisberg, Maurice	St. Paul
‡	Wenzel, Gilbert P.	St. Paul
	Westermeyer, Joseph J.	A.P.O. San Francisco, Calif.
‡	Westover, Darrell E.	St. Paul
	Wetteland, Thomas F.	West St. Paul
‡	Wetzel, Earl V.	St. Paul
‡	Wier, G. Thomas	St. Paul
†‡	Williams, Clayton K.	St. Paul
‡	Williams, George E.	St. Paul
‡	Williams, Hugh J.	St. Paul
‡	Williams, John A.	St. Paul
	Williams, Richard A.	St. Paul Park
	Wilson, Fred B.	St. Paul
‡	Winter, Robert B.	St. Paul
*‡	Witthaus, Melvyn E.	St. Paul
	Wolkoff, Hyman J.	St. Paul
‡	Woodburn, Robert L.	St. Paul
‡	YaDeau, Richard E.	St. Paul
	Youngren, Everett R.	St. Paul
‡	Zachman, Leo L.	St. Paul
	Zagaria, James F.	St. Paul
‡	Zarling, Max E.	St. Paul

RANGE MEDICAL SOCIETY

Koochiching, Itasca and the Northern Portion
of St. Louis County
Regular meetings, fourth Tuesday of the Month
Annual meeting, January
Number of members 107

	PRESIDENT	
	Brockway, Roger W.	Grand Rapids
	SECRETARY	
	Coy, Douglas J.	Grand Rapids
	CORRESPONDING SECRETARY	
	Workman, Mrs. Rae	Hibbing
	Addy, Edward R.	Gilbert
‡	Ahola, Kenneth E.	Hibbing
	Anderson, Russell H.	Virginia
‡	Antonow, Arthur M.	Virginia
	Arko, Frank R.	Hibbing
	Baich, Velemir M.	Coleraine
	Balderson, Robert P.	Grand Rapids
‡	Barnes, Richard E.	Aurora
	Benell, Otto E.	Virginia
†	Binet, Henry E.	Grand Rapids
‡	Birkemeyer, Eugene J.	Ely
‡	Blackmore, Sidney C.	Biwabik
	Bolz, J. Arnold	Grand Rapids
	Bonner, John L.	Grand Rapids
†‡	Bowen, Robert L.	Hibbing
	Braun, Ohrmundt C.	Grand Rapids
	Brockway, Roger W.	Grand Rapids
†	Cantwell, William F.	International Falls
‡	Chermak, Francis G.	International Falls
‡	Ciriacy, Edward W.	Ely
	Cope, Hershel B.	Virginia
‡	Coy, Douglas J.	Grand Rapids
‡	Crow, George M.	International Falls
‡	DeMarais, Lloyd C.	Hibbing
	Dobler, Manfred G.	Ely
‡	Eisenman, Walter	Virginia
†	Engelstad, Wendell P.	Duluth
‡	Erickson, Vernon D.	Grand Rapids
	Evensta, John B.	Grand Rapids
	Ewens, George B.	Virginia
‡	Ferrell, Clarence R.	Grand Rapids
	Fletcher, Robert H.	Chisholm
‡	Flynn, Bernard F.	Hibbing
‡	French, Bayard T.	Hibbing
	Friedlieb, Oskar P.	Virginia
	Gerend, Thomas J.	Virginia
	Glomstad, Gary B.	Deer River
*†‡	Graham, Archibald W.	Chisholm
‡	Grahek, Jack P.	Ely
	Grinley, Andrew V.	Grand Rapids
	Haase, Donald D.	Babbitt
‡	Halper, Bernard	Hibbing
	Halverson, Kermit J.	Parkville
‡	Hanover, Ralph D.	International Falls
‡	Hansen, Robert E.	Hibbing
‡	Heiam, William C.	Cook
	Henwood, Wesley C.	Eveleth
†	Ireland, Gerald W.	St. Paul
	Jacobson, Clarence	Chisholm
*	Joffe, Harold H.	Virginia
‡	Johnson, Calvin J.	Grand Rapids
‡	Johnsrud, Luverne W.	Hibbing
	Johnston, H. Wayne	Virginia
	Karges, Laurel E.	Grand Rapids
	Karish, Louis J.	Grand Rapids
	Kelly, Robert T.	Grand Rapids
	Kiesler, Frank, Jr.	Grand Rapids
‡	Kotchevar, Frank R.	Minneapolis
‡	Kruger, Elmer L., Jr.	Nashwauk
	Law, Harrison E.	Virginia
‡	Lee, William C.	Hibbing
	McKenna, John J.	Virginia
‡	McKenna, Maurice J.	Grand Rapids
	McLeod, John A.	Chisholm
	McQuoid, David W.	Littlefork
*‡	Malmstrom, John A.	Virginia
	Martinson, Raymond M.	Virginia

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Range Medical Society (Continued)

	Mast, Fredric L.	Chisholm
‡	Miettunen, John B.	Hibbing
	Miks, George M.	Eveleth
	Mock, Charles J.	Virginia
*†	Morsman, L. William	Hibbing
‡	Moyer, Richard R.	Hibbing
	Mueller, Donald R.	Grand Rapids
‡	Muller, John J.	Hibbing
‡	Murray, Robert A.	Hibbing
‡	Neff, Walter S.	Virginia
	Nelimark, Donald R.	Virginia
‡	Nollet, Donald J.	Hibbing
	Owens, Ben P.	Hibbing
‡	Paciotti, Vincent J.	Hibbing
‡	Parker, Wilbert H.	Chisholm
	Payne, Richard E.	Virginia
	Perpich, Irene Kosiak	Virginia
	Person, Duane F.	Virginia
	Peterson, Edward N.	Virginia
	Prlina, Isaac M.	Virginia
†	Rajala, Arnold I.	Youngstown, Ohio
	Reed, Paul	Virginia
	Richter, David J.	Virginia
	Roth, Albert H.	Deer River
‡	Rowles, Everett K.	Coleraine
‡	Salter, Reginald A.	Virginia
‡	Schirber, Martin J.	Grand Rapids
‡	Schweiger, Theodore R.	Hibbing
	Sher, David A.	Virginia
	Siegel, John S.	Virginia
†	Sinamark, Andrew	Hibbing
†	Sisler, Clifford E.	Minneapolis
	Snyker, Omer E.	Ely
	Stolen, Keith H.	Grand Rapids
	Summar, M. Thomas	Virginia
‡	Walker, Stuart B.	Aurora
‡	Walter, Frederick H.	International Falls
	Weir, Matthew J.	Virginia
‡	Werner, Donald L.	Aurora
‡	Wheeler, Gilbert S.	Virginia
‡	Will, Charles B.	International Falls
	Wong, Howard H.	Virginia
	Woodruff, Whitney	Virginia

RED RIVER VALLEY MEDICAL SOCIETY

Kittson, Mahnomen, Marshall, Norman, Pennington, Polk,
Red Lake and Roseau Counties
Regular meetings quarterly
Annual meeting, December
Number of members 57

PRESIDENT
Hunt, Vincent R. .... Red Lake Falls

SECRETARY
Sather, Russell O. .... Crookston

	Anderson, Roland G.	Thief River Falls
‡	Anderson, Wallace E.	Clearbrook
	Baab, Robert O.	Crookston
‡	Behr, Orlo K.	Crookston
‡	Berg, Arnold M.	Thief River Falls
†	Bratrud, Edward	Alexandria
	Brink, Adlai A.	Baudette
‡	Brown, Glenn W.	Halstad
	Cameron, John H.	Clovis, New Mexico
‡	Clapp, Hubert D.	Crookston
	Collins, Roger T.	Roseau
	Cotton, Gerald E.	Fosston
‡	Covey, Kenneth W.	Crookston
	Dagg, Earl	Thief River Falls
	Davidson, Duane J.	Thief River Falls
‡	Delmore, John L.	Roseau
†‡	Flancher, Leon H.	Detroit Lakes
‡	Foderick, Peter P.	Hallock
*‡	Greene, Daniel E.	Warren
‡	Herber, Leo	Thief River Falls
‡	Hirsch, Stanton	Crookston
	Holm, Owen W.	Crookston
‡	Holmstrom, Carle H.	Warren
	Hunt, Vincent R.	Red Lake Falls
	Janecky, Allen G.	Baudette
‡	Jensen, John A.	Crookston
‡	Kinkade, Byron R.	Ada
‡	Klefstad, Lloyd H.	Greenbush
‡	Kostick, William R.	Fertile
	Leonardson, Peter Y.	Red Lake Falls
‡	Loken, Theodore	Ada
†	Lynde, Orrin G.	Los Gatos, California
‡	Martin, George B.	Thief River Falls
	Mercil, Charles B.	Mahnomen
‡	Mercil, William F.	Crookston
†	Nelson, Henry E.	Crookston
‡	Oppegaard, C. L.	Crookston
	Overland, Arnold J.	Rolla, No. Dak.
‡	Pumala, Erven E.	Warren
‡	Reff, Alan R.	Crookston
‡	Roholt, Christian L.	McIntosh
	Rubin, Jacob S.	Crookston
	Russ, Homer H.	Warroad
	Sather, Edgar L.	Fosston
‡	Sather, George A.	Fosston
‡	Sather, Richard N.	Fosston
‡	Sather, Russell O.	Crookston
‡	Scheuneman, Allen F.	Thief River Falls
‡	Schnabel, Robert F.	Crookston
‡	Skogerboe, Rudolph B.	Minneapolis
‡	Stadem, Clifford J.	Twin Valley
‡	Stewart, Donald E.	Crookston
‡	Thorsgard, Ernest O.	Thief River Falls
‡	Thysell, Harold R.	Crookston
‡	Uhley, Charles G.	Crookston
‡	Van Rooy, George T.	Thief River Falls
‡	Wendt, H. Paul	Thief River Falls
‡	Wikoff, Howard M.	Crookston

RENVILLE-REDWOOD COUNTY MEDICAL SOCIETY

Renville and Redwood Counties
Regular meetings, third Tuesday of each month
Annual meeting, December
Number of members 17

PRESIDENT
Hable, Orville A. .... Buffalo Lake
SECRETARY
Diessner, Ardell W. .... Redwood Falls
Alcorn, William J. .... Wabasso
‡ Anderson, Chester A. .... Hector
‡ Bingham, George C. .... Bird Island
† Brand, William A. .... Redwood Falls
‡ Ceplecha, Stanley F. .... Redwood Falls
‡ Cosgriff, James A. .... Olivia
Cosgriff, James A., Jr. .... Olivia
‡ Diessner, Ardell W. .... Redwood Falls
‡ Fawcett, Arthur M. .... Renville
‡ Flinn, James B. .... Redwood Falls
‡ Furr, Leo O. .... Bird Island
‡ Hable, Orville A. .... Buffalo Lake
†‡ Inglis, William .... Milwaukee, Wis.
Lenz, Joseph R. .... Morton
‡ Nelson, Glenn E. .... Fairfax
†‡ Rud, James A. .... Sioux Falls, S. D.
‡ Strauchler, John .... Belview

RICE COUNTY MEDICAL SOCIETY

Rice County
Regular meetings quarterly
Annual meeting in December
Number of members 32

PRESIDENT
Halvorson, David C. .... Northfield
SECRETARY
Searl, Richard H. .... Faribault
‡ Bauer, Paul G. .... Faribault
‡ Beaton, J. Gordon .... Northfield
‡ Bruhl, Heinz H. .... Faribault
Buesgens, Ralph H. .... Waterville
Clarke, Dean T. .... Faribault
‡ Engberg, Edward J. .... Faribault
Francis, David W. .... Morristown
Glesne, Otto N. .... Northfield
‡ Good, Roy H. .... Northfield
‡ Graham, Asa B. .... Faribault
‡ Haas, Jack F. .... Northfield
‡ Halvorson, David C. .... Northfield
Hanson, J. W. .... Northfield
Kennedy, George L. .... Faribault
‡ Kolars, James J. .... Faribault
Lende, Norman .... Faribault
Meyer, Frederick C. .... Faribault
Meyer, Paul F. .... Faribault
Meyer, Richard H. .... Faribault
Meyer, Robert P. .... Faribault
‡ Nuetzman, Arthur W. .... Faribault
‡ Orr, Burton A. .... Faribault
Rumpf, Carl W. .... Faribault
‡ Rysgaard, George N. .... Northfield
‡ Searl, Richard H. .... Faribault
‡ Smith, Thorsten .... Faribault
‡ Speckals, Robert C. .... Faribault
‡ Street, Bernard .... Northfield
Studer, Donald J. .... Faribault
Thomson, James M. .... Faribault
† Traeger, Carl A. .... Faribault
‡ Watts, George W. .... Faribault
‡ Weaver, Paul H. .... Faribault

ST. LOUIS COUNTY MEDICAL SOCIETY

Carlton, Cook, Lake and Southern portion of
St. Louis County
Regular meetings, second Thursday in each month
except July and August
Annual meeting, second Thursday in January
Number of members 205

PRESIDENT
Bagley, Charles M. .... Duluth
SECRETARY
Dwyer, John J. .... Duluth
SECRETARY, EXECUTIVE OFFICE
Lundgren, Miss Margaret M. .... Duluth
Anderson, James M. .... Duluth
‡ Abraham, Arden L. .... Duluth
‡ Ahrens, Curtis F. .... Duluth
‡ Asta, Joseph J. .... Duluth
† Athens, A. G. .... Santa Barbara, California
‡ Atmore, William G. .... Duluth
‡ Aufderheide, Arthur C. .... Duluth
‡ Backus, Byron C. .... Cloquet
‡ Backus, Lloyd B. .... Cloquet
‡ Backus, Reno W. .... Nopeming
‡ Bagley, Charles M. .... Duluth
Bagley, Elizabeth C. .... Duluth
*†‡ Bagley, William R. .... Duluth
‡ Bakkila, Henry E. .... Duluth
‡ Balmer, Albert I. .... Duluth
‡ Bardon, Richard .... Duluth
‡ Barker, John D. .... Duluth
† Barney, Leon A. .... Duluth
‡ Barrett, Earl E. .... Duluth
‡ Bartzen, Peter J. .... Duluth
‡ Becker, Frederic T. .... Duluth
‡ Bell, Harry M. .... Duluth
Bepko, Marie K. (Mrs. Puumala) .... Cloquet
Berdez, George L. .... Duluth
‡ Bergan, Robert O. .... Duluth
‡ Bianco, Anthony J. .... Duluth
‡ Bloom, Joseph .... Silver Bay

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St. Louis County Medical Society (Continued)

‡	Boecker, Bernhard	Duluth
	Boman, Paul G.	Duluth
‡	Boyer, Samuel H.	Duluth
‡	Bray, Philip N.	Duluth
‡	Brooker, Warren J.	Duluth
	Brown, Cyrus C.	Duluth
‡	Buckley, Robert P.	Duluth
‡	Butler, John K.	Cloquet
†	Campaigne, Robert J.	Duluth
‡	Christensen, Clarence H.	Duluth
	Church, Gerald E.	Two Harbors
	Clark, Elizabeth A. (Mrs. Halbert)	Duluth
‡	Clark, Ivan T.	Duluth
‡	Coll, James J.	Duluth
†	Collins, Arthur N.	Duluth
‡	Conley, Francis W.	Duluth
‡	Coventry, William D.	Duluth
‡	Cowan, George M.	Duluth
‡	Creps, James R.	Duluth
	Davis, William I.	Moose Lake
‡	Deutsch, Robert J.	Duluth
‡	Dickson, Franklin H.	Proctor
‡	Dietrich, Donald E.	Duluth
‡	Dobbs, Richard L.	Duluth
‡	Dwyer, John J.	Duluth
‡	Eckman, Philip F.	Duluth
	Eckman, Philip L.	Duluth
‡	Eckman, Ralph J.	Duluth
*†	Ekblad, John W.	Rock Island, Ill.
‡	Eklund, Carl D.	Duluth
‡	Elias, Frank J.	Duluth
‡	Emanuel, Karl W.	Duluth
	Eppard, Raymond M	Cloquet
	Evison, Emerson O.	Duluth
‡	Fawcett, Keith R.	Duluth
‡	Fellows, Manley F.	Duluth
‡	Feuling, John C.	Duluth
‡	Fifield, Malcolm McC.	Duluth
‡	Fischer, Mario M.	Duluth
‡	Fisketti, Henry	Duluth
‡	Fuller, Josiah	Duluth
‡	Gillespie, Malcolm G.	Duluth
†	Gobel, Fredarick L.	Minneapolis
‡	Goldish, Daniel R.	Duluth
‡	Goldish, Robert J.	Duluth
‡	Goldschmidt, Volker	Duluth
‡	Goodnow, William H.	Duluth
‡	Gowan, Lawrence R.	Duluth
	Gowan, Lawrence R., Jr.	Duluth
‡	Grohs, William H.	Duluth
‡	Gronquist, Y. K. J.	Cloquet
‡	Haavik, John E.	Duluth
	Halbert, John J.	Duluth
‡	Halliday, Phillip V.	Duluth
	Hanson, Ernest O.	Cloquet
‡	Harrington, Vernon A.	Duluth
	Heisel, John G.	Duluth
†	Helwig, Karl L.	Duluth
‡	Hilding, Anderson C.	Duluth
†	Hill, Frederick E.	Riverside, California
†	Hirschboeck, Frank J.	Duluth
‡	Hoeg, Dwight C.	Duluth
‡	Hoff, Herbert O.	Duluth
	Holt, Glen E.	Duluth
‡	Houkom, S. Sverre	Duluth
	Hutchinson, Henry	Moose Lake
	Jacklin, Alexander J.	Duluth
‡	Jacobson, Ferdinand C.	Duluth
	Jacott, William E.	Duluth
†	Jensen, Thorvold J.	Duluth
‡	Jeronimus, Henry J.	Duluth
	Jessico, Charles M.	Duluth
‡	Johnson, Franklin L.	Duluth
‡	Johnson, Karl E.	Duluth
	Johnson, Theodore L.	Duluth
†	Jorgenson, Edward O	Rochester
‡	Juntunen, Roy R.	Duluth
	Kilen, Mark	Duluth
†‡	Klein, Harry	Duluth
‡	Klein, William A.	Duluth
‡	Knoedler, John P.	Duluth
	Kohlbry, Carl O.	Duluth
	Kosiak, William	Two Harbors
‡	Krueger, Victor R.	Nopeming
	Kundel, Donald W.	Duluth
‡	L'Abbe, A. J. Philip	Duluth
	L'Esperance, Bernard F.	Two Harbors
	LaBree, Robert H.	Duluth
‡	Langseth, Rodney N.	Duluth
‡	Larson, Donald M.	Duluth
	Larson, Keith D.	Moose Lake
	Larson, Kenneth R.	Moose Lake
‡	Latterell, Kenneth E.	Duluth
‡	Leek, Joseph H.	Duluth
†	Lepak, Francis J.	Duluth
	Leppink, Harold B.	Two Harbors
	Leppo, N. Erkki A.	Duluth
	Linke, Charles A.	Duluth
	Linke, Clara L.	Duluth
‡	Litman, Samuel N.	Duluth
†‡	McNutt, John R.	Duluth
	MacDonald, Roger A.	Grand Marais
‡	MacRae, Gordon C.	Duluth
†‡	Magney, Fredolph H.	Duluth
	Martin, Webster C.	Duluth
‡	Maryland, Daniel L.	Duluth
†	Mayne, Roy M.	St. Paul
	Mendesh, Anthony N.	Duluth
‡	Merrick, William G.	Duluth
‡	Meyer, Howard J.	Duluth
	Michaelis, Dorothy L.	Duluth
†	Moe, Thomas	Moose Lake
	Monge', James J.	Duluth
	Moller, Julie C.	Duluth
‡	Monserud, Nels O.	Cloquet
‡	Moyer, John B.	Duluth
‡	Munger, James E.	Duluth
	Munson, Martin S.	Moose Lake
‡	Nisius, George F.	Duluth
‡	Nisswandt, Albert L.	Duluth
†‡	Norberg, Carl E.	Los Altos, Calif.
‡	O'Neill, John C.	Duluth
*‡	Olson, Archie O.	Duluth
‡	Pasek, Antone W.	Cloquet
‡	Patch, Orien B.	Duluth
‡	Pedersen, Roy C.	Duluth
‡	Peterson, John H.	Duluth
‡	Pollard, William S.	Duluth
‡	Power, John E.	Duluth
	Puumala, Barbara M.	Cloquet
	Puumala, Reino H.	Cloquet
	Puumala, Ricard R.	Cloquet
‡	Reardon, Andrew E.	Duluth
‡	Reed, Henry H.	Duluth

St. Louis County Medical Society (Continued)

	Rondeau, Eugene T.	Two Harbors
	Rosenquist, Rudolph J.	Silver Bay
	Rowe, Richard G.	Silver Bay
‡	Rudie, Peter S.	Duluth
‡	Rudie, William D.	Duluth
‡	Runquist, John M.	Duluth
‡	Ruth, Bradley R.	Duluth
	Ryan, Edward A.	Duluth
	Sach-Rowitz, Alvan	Moose Lake
	Saloum, Lucille M.	Duluth
	Sanford, John B.	Duluth
*†	Sarff, Oliver E.	Duluth
	Sax, Milton H.	Duluth
	Sax, Simon G.	Duluth
‡	Schmid, John F.	Duluth
‡	Schneider, Lawrence E.	Duluth
‡	Shirley, Raymond M.	Duluth
	Slack, William J.	Duluth
‡	Smith, Cyril M.	Duluth
	Smith, Wallace R.	Grand Marais
‡	Spang, Anthony J.	Duluth
‡	Spang, James S.	Duluth
‡	Spang, W. M.	Duluth
‡	Stein, William A.	Duluth
‡	Storsteen, Kenneth A.	Duluth
‡	Streitz, John M.	Duluth
‡	Strewler, Gordon J.	Duluth
‡	Swedberg, William A.	Duluth
‡	Swensen, Don P.	Duluth
‡	Swenson, Arnold O.	Duluth
‡	Teich, Kenneth W.	Chicago, Ill.
‡	Terrell, Bernard J.	Nopeming
‡	Tetlie, James P.	Duluth
‡	Thomas, John V.	Duluth
‡	Thurn, Roy J.	Duluth
‡	Tosseland, Noel E.	Duluth
†	Trautmann, James C.	Rochester
	Ulrich, Emery E.	Duluth
	Van Druten, William A.	Duluth
	Van Puffelen, Paul S.	Duluth
	Van Ryzin, Donald J.	Duluth
‡	Walder, Harold J.	Duluth
‡	Wall, Jack E.	Duluth
‡	Wallace, Martin O.	Duluth
	Wells, Arthur H.	Duluth
‡	Williams, Bruce F. P.	Duluth
†	Winter, John A.	Duluth
‡	Wolfe, John W.	Duluth
‡	Young, Hadley R.	Duluth
‡	Young, Thomas O.	Duluth
‡	Zemmers, Robert	Duluth

SCOTT-CARVER COUNTY MEDICAL SOCIETY

Scott and Carver Counties
Regular meetings, First Tuesday of each month
Annual meeting in June
Number of members 42

PRESIDENT
Hallgren, Roger B. .... Belle Plaine
SECRETARY
Adams, Patrick J. .... Shakopee

‡	Adams, Patrick J.	Shakopee
	Bean, Charles N.	Waconia
‡	Bratholdt, James W.	Watertown
†	Buck, Frederick H.	Shakopee
‡	Cervenka, Charles F.	New Prague
‡	Clarke, John W.	Waconia
†‡	Daly, Alfred E.	Burnsville
‡	Doherty, Elmer M.	New Prague
‡	Erickson, Robert L.	Rosemount
‡	Field, Anthony H.	Savage
‡	Gildersleeve, Robert G.	Watertown
‡	Hallgren, Roger B.	Belle Plaine
†	Hebeinsen, Milton B.	Chaska
	Heinz, Ivy	Shakopee
‡	Heinzerling, Carl R.	Chaska
†‡	Juergens, Herman M.	Belle Plaine
†	Kucera, Stanley T.	Northfield
‡	Kuz, Eugene	Savage
‡	Larson, Leighton W.	Waconia
‡	Lehrer, Alfred J., Jr.	Montgomery
‡	Lukk, Olaf	Prior Lake
	McDaniel, Samuel P.	Lakeville
‡	Mendiola, Ramon P., Jr.	Waconia
†‡	Moller, Jurgen	Farmington
‡	Nelson, Gerald E.	Chaska
*†	Novak, Edward E.	New Prague
‡	Olson, Richard E.	Chaska
‡	Pearson, Bror F.	Shakopee
‡	Philp, David R.	Watertown
‡	Pistulka, R. D.	Chaska
‡	Ponterio, James E.	Shakopee
	Rieschl, Elizabeth K.	Jordan
‡	Rynda, Edwin R.	New Prague
‡	Schimelpfenig, George T.	Chaska
‡	Schwartz, Robert K.	Chaska
‡	Smith, David G.	Watertown
‡	Spagnolo, Anthony A.	Shakopee
‡	Splettstoesser, Robert W.	Belle Plaine
	Stahler, Paul A.	Jordan
‡	Tuma, Ben	Waconia
‡	Wempner, Jon D.	Waconia
†‡	Westerman, Alvin S.	Montgomery
†‡	Westerman, Fred C.	Montgomery

SOUTHWESTERN MINNESOTA MEDICAL SOCIETY

Cottonwood, Jackson, Murray, Nobles, Pipestone
and Rock Counties
Regular meetings, first Monday of each month except
July and August
Annual meeting, November
Number of members 58

	PRESIDENT	
	Boone, Ervin S.	Luverne
	SECRETARY	
	Heiberg, O. M.	Worthington
‡	Amick, Arthur E.	Worthington
‡	Bader, J. L.	Slayton
‡	Basinger, Harold P.	Windom
‡	Basinger, Homer P.	Windom
‡	Beckering, Gerrit	Edgerton
‡	Beckering, Roland G.	Edgerton
‡	Benjamin, Walter G.	Pipestone
‡	Bofenkamp, Ferdinand W.	Luverne
‡	Boone, Ervin S.	Luverne
‡	Boyd, Frank E.	Pipestone
‡	Buresh, Kenneth L.	Westbrook
‡	Carlson, John V.	Westbrook
‡	Carlson, Lloyd E.	Worthington
‡	Christiansen, Harold A.	Jackson
‡	Daumann, Roy E.	Jackson
‡	Dawson, Lorin D.	Worthington
‡	Desai, B. J.	Worthington
‡	Dokken, James H.	Windom
‡	Doman, Victor W.	Lakefield
‡	Faul, Bennie C.	Worthington
‡	Fitch, Charles G.	Worthington
†‡	Halloran, Walter H.	Jackson
‡	Halpern, David J.	Brewster
‡	Harrison, Percy W.	Worthington
‡	Hegstad, Thomas C.	Windom
‡	Heiberg, Olaf M.	Worthington
‡	Hoyer, Ludolf J.	Windom
†	Jaeger, Dwight E.	Minneapolis
‡	Johnson, Alan R.	Windom
‡	Keyes, Robert W.	Pipestone
‡	Kilbride, Edwin A.	Worthington
‡	Kotval, Russell J.	Pipestone
‡	Laikola, Leslie A.	Adrian
‡	Larsen, Russell H.	Lakefield
‡	Lohmann, John G.	Pipestone
‡	McNear, George R., Jr.	Heron Lake
‡	Maitland, Edwin T.	Jackson
‡	Martin, Albert	Luverne
‡	Minge, Raymond K.	Worthington
‡	Nealy, Donald E.	Adrian
‡	Nywall, Dean D.	Slayton
‡	Odland, Donald M.	Luverne
‡	Patterson, Hugh D.	Slayton
‡	Pierce, Robert B.	Mountain Lake
‡	Pierson, Roy F.	Slayton
†‡	Piper, William A.	Mountain Lake
‡	Plucker, Milton W.	Worthington
‡	Rud, Paul D.	Luverne
‡	Ryding, Vincent	Ames, Iowa
‡	Seisler, Edward P.	Worthington
†‡	Sherman, Charles L.	Luverne
‡	Siebert, Darrel W.	Luverne
‡	Stam, John	Worthington
‡	Strand, Jack W.	Jasper
‡	Stratte, Harold C.	Windom
‡	Wells, Walter B.	Jackson
‡	Wiens, Alvin L.	Mountain Lake
†	Williams, Charles A.	Seattle, Washington

STEARNS-BENTON COUNTY MEDICAL SOCIETY

Stearns and Benton Counties
Regular meetings, third Thursday of each month
Annual meeting December
Number of members 84

	PRESIDENT	
	Broker, Henry M.	St. Cloud
	SECRETARY	
	Sommers, Stephen D.	St. Cloud
‡	Alden, Charles W.	Kimball
	Aulick, Ernest J.	Paynesville
‡	Autrey, William A.	St. Cloud
	Ballantine, Jerome J.	St. Cloud
	Barnett, Arthur J.	Foley
‡	Baumgartner, Florian H.	Albany
‡	Berger, Phil R.	St. Cloud
‡	Beuning, John B.	St. Cloud
‡	Bozanich, Milosh S.	St. Cloud
	Brattensborg, Henry J.	St. Cloud
‡	Brigham, Charles F., Jr.	St. Cloud
‡	Broker, Henry M.	St. Cloud
	Brown, Frank T.	St. Cloud
*†‡	Buscher, Julius C.	St. Cloud
	Carter, Donald C.	St. Cloud
‡	Cesnik, Robert J.	Sauk Rapids
†‡	Clark, Harry B.	St. Cloud
	Cleaves, William D.	Sauk Centre
	Cumming, Robert J.	St. Cloud
‡	Donaldson, Charles S.	St. Cloud
	DuBois, Julian F.	Sauk Centre
‡	Dziubinski, Emil H.	St. Cloud
‡	Evans, Leslie M.	Sauk Rapids
‡	Gaida, Joseph B.	St. Cloud
‡	Gerstenkorn, George B.	Milaca
	Grant, John C.	St. Cloud
	Halenbeck, Philip L.	St. Cloud
	Harbaugh, John T.	St. Cloud
	Hedenstrom, Paul H.	St. Cloud
†	Henry, Clarence J.	Onamia
	Henry, Joseph E.	Milaca
	Higdon, Donald A.	St. Cloud
‡	Hughes, Bernard J.	St. Cloud
	John, Byron L.	St. Cloud
†‡	Jones, Richard N.	St. Cloud
	Keith, Paul J.	Milaca
‡	Kelly, James H.	St. Cloud
‡	Kelly, John F.	Cold Spring
‡	Koenig, Robert P.	St. Cloud
	Kuhlmann, Lawrence B.	Melrose
	Kvistberg, Gerald K.	St. Cloud

Stearns-Benton County Medical Society (Continued)

‡	LaFond, Edward M.	St. Cloud
‡	Lenarz, Albert J.	St. Cloud
	Lindeman, Raymond J.	Paynesville
‡	Lindley, Stanley B.	St. Cloud
‡	Loeb, George	St. Cloud
‡	Loes, Louis A.	St. Cloud
†‡	McDowell, John P.	St. Cloud
	McNamara, John P.	Rice
‡	May, Robert B.	St. Cloud
‡	Milhaupt, Emmett N.	St. Cloud
	Moran, Paul T.	St. Cloud
	Mueller, Rudolph B.	Richmond
‡	Murn, Thomas G.	St. Cloud
‡	Murray, Robert A., Jr.	St. Cloud
	Myre, Clifford R.	Paynesville
	Nietfield, Aloys B.	Sauk Centre
‡	O'Keefe, James P.	St. Cloud
‡	Olinger, John N.	St. Cloud
‡	Petersen, Robert T.	St. Cloud
‡	Phares, Otto C.	St. Cloud
‡	Raetz, Sylvester J.	Maple Lake
‡	Reif, Henry J.	St. Cloud
‡	Rice, William H.	St. Cloud
‡	Richards, William B.	St. Cloud
	Ritchie, Donald A.	St. Cloud
‡	Rozycki, Anthony T.	St. Cloud
	Salk, Richard J.	Albany
	Savelkoul, Gene R.	Belgrade
‡	Schmitz, Everett J.	St. Cloud
	Smith, J. Weston	St. Cloud
	Sisk, Harvey E.	St. Cloud
‡	Sommers, Stephen D.	St. Cloud
‡	Stiles, Clifford D.	Foley
‡	Thienes, R. Lawrence	St. Cloud
‡	Thuringer, Carl B.	St. Cloud
	Undem, Dale	St. Cloud
	Vanderpool, Thomas E.	Paynesville
‡	Veranth, Leonard A.	St. Cloud
‡	Wenner, Waldemar T.	St. Cloud
‡	Wittrock, Louis H.	Watkins
	Zachman, Albert H.	Melrose
	Zachman, John F.	Melrose
‡	Zeleny, Joseph H.	St. Cloud

STEELE COUNTY MEDICAL SOCIETY

Steele County
Regular meetings, Third Tuesday of
March, May, September, November and January
Annual meeting, January
Number of members 23

PRESIDENT
Halvorsen, Daniel K. . . . . Owatonna
SECRETARY
Adams, Brandon L. W. . . . . Owatonna

	Adams, Brandon L. W.	Owatonna
‡	Anderson, Franklin C.	Owatonna
	Arnesen, John F.	Owatonna
‡	deWerd, Robert W.	Owatonna
	Dewey, Donald H.	Owatonna
‡	Fischer, John R.	Blooming Prairie
‡	Floersch, Adrian J.	Owatonna
‡	Halvorsen, Daniel K.	Owatonna
	Hartung, Elmer H.	Claremont
‡	Henry, John C.	Owatonna
‡	Henry, Kenneth G.	Owatonna
‡	Hilker, Robert T.	Owatonna
	Honath, Donald H.	Owatonna
	Kulstad, Oscar S.	Dodge Center
	Lundquist, Curt W.	Owatonna
‡	McEnaney, James E.	Owatonna
†	McIntyre, John A.	Owatonna
†	Morehead, Dewey E.	Bodega Bay, California
‡	Olson, Albert J.	Owatonna
	Roberts, Oliver W.	Owatonna
	Schaefer, Joseph F.	Owatonna
	Stransky, Theodore W.	Owatonna
†	Wilkowske, Rudolph J.	Owatonna

UPPER MISSISSIPPI MEDICAL SOCIETY

Aitkin, Beltrami, Cass, Clearwater, Crow Wing, Hubbard,
Lake of the Woods, Morrison, Todd and Wadena Counties
Regular meetings, January, May and September
Annual meeting January
Number of members 98

PRESIDENT
Adkins, James T. . . . . Bertha
SECRETARY
Anderson, Arden O. . . . . Brainerd

‡	Adkins, James T.	Bertha
‡	Aga, John H.	Brainerd
‡	Anderson, Arden O.	Brainerd
†	Anderson, Werner W.	Cincinnati, Ohio
†‡	Badeaux, George I.	Brainerd
‡	Belcher, Royden A.	Little Falls
‡	Bender, James H.	Brainerd
‡	Benson, Alfred H.	Little Falls
‡	Bissinger, Lester L.	Brainerd
†	Bolstad, Owen C.	Ft. Snelling
‡	Borgerson, Arthur H.	Long Prairie
‡	Brown, Russell T.	Browerville
	Burman, Richard E.	Aitkin
‡	Cardle, George E.	Brainerd
	Closuit, Frederick C.	Aitkin
‡	Coombs, Carl H.	Cass Lake
†	Craig, C. C.	International Falls
	Crow, Earl R.	Minnetonka
	Davis, Lloyd T.	Wadena
	Davis, Luther F.	Wadena
	Deweese, Wilford J.	Bemidji
†	Dillenburg, C. J.	Grand Forks, N. D.
‡	Dodson, Albertus F.	Brainerd
†‡	Duthoy, E. J.	Bloomington
‡	Erickson, Alvin O.	Long Prairie
‡	Fitzsimons, William E.	Brainerd

Continued on Next Page

Upper Mississippi Medical Society (Continued)

	Fortier, George M. A.	Little Falls
‡	Gamm, Edgar R.	Park Rapids
†	Ghostley, Mary C.	Fullerton, Calif.
	Gregoire, Earl	Bemidji
	Griffin, John W.	Bemidji
	Grimes, Paul T.	Park Rapids
	Groschupf, Richard P.	Bemidji
†	Groschupf, Theophilus P.	Bemidji
‡	Grose, Frederick N.	Clarissa
†	Hall, George M.	Rochester
	Halme, William B.	Wadena
	Hansen, Milo L.	Little Falls
	Hartjen, Jason K.	Bemidji
	Haugen, Norman R.	Park Rapids
†	Healy, Raymond T.	Pierz
	Heid, James K.	Little Falls
	Hendricks, Esten J.	Verndale
	Henry, Richard T.	Titusville, Fla.
	Hildebrand, John E.	Bemidji
	Hoganson, Donald E.	Bemidji
‡	Johnson, Douglas L.	Little Falls
†	Johnson, Einer W.	Bemidji
‡	Kanne, Earl R.	Brainerd
‡	Kelley, Roger E.	Crosby
	Knipp, William J.	Brainerd
	Knoll, W. V.	Brainerd
	Larson, Leroy J.	Bagley
‡	Lee, Hubert W.	Brainerd
†	Lofstrom, Dennis E.	St. Paul
	Longfellow, Helen W.	Brainerd
	Lund, Werner J.	Staples
	Lundsten, Leslie C.	Bemidji
‡	McLane, William O.	Brainerd
‡	Marshall, Clark M.	Crosby
‡	Marvin, Joseph E.	Brainerd
‡	Meller, Maurice	Brainerd
	Mortenson, Howard O.	Menahga
‡	Mosby, Maurice E.	Long Prairie
‡	Mulligan, Arthur M.	Brainerd
	Ness, Duane E.	Wadena
‡	Nixon, James B.	Crosby
	Nordlund, Mildred E.	McClellan A.F.B. Calif.
‡	O'Leary, John B.	Brainerd
	Olson, Lillian A.	Bemidji
	Palmer, Harry A.	Blackduck
	Parker, Charles W.	Wadena
	Parker, Warren E.	Sebeka
‡	Pedersen, Robert L.	Brainerd
‡	Pelzl, Charles R.	Pine River
	Petraborg, Harvey T.	Aitkin
	Pettersen, George R.	Aitkin
‡	Poppie, Robert W.	Brainerd
	Reeber, Erick	Bagley
‡	Reichelderfer, Charles F.	Staples
‡	Reichelt, Leland G.	Wadena
	Rhodes, Clinton E.	Park Rapids
‡	Ringle, Otto F.	Walker
	Roholt, Hartvig B.	Bemidji
	Scanlon, Hugh A.	Little Falls
†	Schrantz, Robert D.	Phoenix, Ariz.
†	Schulberg, Verne A.	Minneapolis
	Seifert, Donald R.	Little Falls
	Spieler, F. B.	Pequot Lakes
‡	Stein, Raymond J.	Pierz
	Stoy, Robert A.	Little Falls
†	Thompson, James R.	Rochester
‡	Watson, Sidney W.	Royalton
‡	Westley, Kent F.	Little Falls
	Whittemore, Dexter D.	Bemidji
	Wiger, Oliver E.	Little Falls
†	Will, William W.	Bertha
‡	Williams, Mervyn M.	Ah-Gwah-Ching
	Witter, Robert L.	Wadena

WABASHA COUNTY MEDICAL SOCIETY

Wabasha County
Regular meetings, special call
Annual meeting first Thursday after first Monday in October
Number of members 13

PRESIDENT
Martin, David E., III . . . . Wabasha
SECRETARY
Gjerde, William P. . . . . Lake City

‡	Bayley, E. Covell	Lake City
‡	Bouquet, Bertram J.	Wabasha
‡	Bowers, Robert N.	Lake City
‡	Ekstrand, LeRoy M.	Wabasha
‡	Ellis, Earl W.	Elgin
‡	Gjerde, William P.	Lake City
†	Habein, Harold C.	Palo Alto, Calif.
‡	Mahle, Donald G.	Plainview
‡	Martin, David E., III	Wabasha
	Martin, Doreen A.	Pepin, Wisconsin
	Ochsner, Clarence G.	St. Paul
†	Replogle, William H.	Los Angeles, California
‡	Sontag, David W.	Lake City

WASECA COUNTY MEDICAL SOCIETY

Waseca County
Regular meetings, Bimonthly
Annual meeting, January
Number of members 7

PRESIDENT
Olds, George H. . . . . New Richland
SECRETARY
Normann, Stephen T. . . . . Waseca

‡	Davis, Raymond D.	Belmont, California
‡	Hottinger, Raymond C.	Janesville
‡	Normann, Stephen T.	Waseca
‡	Oeljen, Siegfried C. G.	Waseca
‡	Olds, George H.	New Richland
‡	Rohrer, Thomas P.	Waseca
‡	Swenson, Orvie J.	Waseca

WASHINGTON COUNTY MEDICAL SOCIETY

Washington and Dakota Counties
Regular meetings, second Tuesday in each month
Annual meeting, December
Number of members 32

PRESIDENT	
Zeller, Hector C.	Hastings
SECRETARY	
Stratte, Jon R.	Stillwater
‡ Bealka, Neil	Stillwater
Brabec, Paul F.	Hastings
‡ Carlson, Russel E.	Stillwater
Cowger, Robert R.	Farmington
Dale, Les N.	Hastings
Eiden, Vera M.	Stillwater
Fasbender, Herman T.	Hastings
Foderick, John W.	Hastings
Hegrenes, Robert L.	Farmington
† Holcomb, Joel T.	Marine-on-St. Croix
‡ Jenson, James E.	Stillwater
‡ Johnson, O. Guy	Bayport
‡ Johnson, Robert H.	Bayport
‡ Juergens, Manley F.	Stillwater
Just, Herman J.	Hastings
‡ Kiolbasa, Edward B.	Stillwater
Kleinsasser, Warren L.	Farmington
Kulzer, Norbert J.	Hastings
‡ McCarten, Francis M.	Stillwater
Midboe, Gilbert T.	Forest Lake
‡ Murphy, Thomas R.	Stillwater
Peikert, Carl F.	Forest Lake
Peterson, John O.	Hastings
† Poirier, Joseph A.	St. Paul
Ruggles, George M.	Forest Lake
‡ Sherman, Carnot H.	Bayport
‡ Stratte, Jon R.	Stillwater
†‡ Stuhr, John W.	Stillwater
† Torghele, John R.	Hastings, Nebraska
Van Meier, Henry	Stillwater
Weiss, Carl A.	Hastings
Zeller, Hector	Hastings

WEST CENTRAL MINNESOTA MEDICAL SOCIETY

Big Stone, Pope, Stevens and Traverse Counties
Regular meetings, second Tuesday in March, May, September and November
Annual meeting, November
Number of members 25

PRESIDENT	
Kozel, William J.	Morris
SECRETARY	
Winge, H. C.	Wheaton
‡ Arneson, Arthur I.	Morris
†‡ Behmler, Frederick W.	Morris
† Bergan, Otto	Clinton
‡ Brace, Ray I.	Clinton
‡ Bucher, Foster D.	Starbuck
‡ Christenson, Carl E.	Clinton
‡ Eide, O. A.	Hancock
‡ Hedemark, Homer H.	Ortonville
Hedemark, Truman A.	Ortonville
Karn, Jacob F.	Ortonville
Knip, Robert J.	Ortonville
‡ Kolp, Berton A.	Glenwood
‡ Kooda, Jennings C.	Morris
‡ Kozel, William J.	Morris
‡ Lee, Gordon E.	Glenwood
†‡ Letson, Robert D.	Minneapolis
*‡ Lindberg, Alfred L.	Wheaton
‡ Magnuson, Allen E.	Wheaton
† Merrill, Robert W.	Minneapolis
‡ Oliver, Irwin L.	Graceville
‡ Popoff, Russel G.	Graceville
‡ Rossberg, Raymond A.	Morris
‡ Swedenburg, Paul A.	Glenwood
‡ Vangerud, Paul T.	Wheaton
Watson, Robert M.	Morris
‡ Winge, H. C.	Wheaton
‡ Zempel, Alan R.	Starbuck

WINONA COUNTY MEDICAL SOCIETY

Winona County
Regular meetings, second Monday in January, April, July and October
Annual meeting, January
Number of members 29

PRESIDENT	
Degallier, Daniel	Winona
SECRETARY	
Heise, Herbert vR.	Winona
‡ Boardman, Dalmon V.	Winona
‡ Christensen, Eli E.	Winona
‡ Degallier, Daniel	Winona
‡ Fenske, Arnold	Winona
‡ Finkelnburg, William	Winona
‡ Garber, George L.	Winona
‡ Haesly, Warren W.	Winona
‡ Hartwich, Roger F.	Winona
‡ Hawk, Dale J.	St. Charles
Heise, Carl vR.	Winona
‡ Heise, Herbert vR.	Winona
‡ Heise, Paul vR.	Winona
‡ Heise, Philip vR.	Winona
‡ Heise, William vR.	Winona
‡ Hughes, Sidney O.	Winona
‡ Johnson, Curtis M.	Winona
‡ Johnston, Leonard	Winona
†‡ Keyes, John D.	Winona
‡ Loomis, George L.	Winona
†‡ McLaughlin, Edmund M.	Winona

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Winona County Medical Society (Continued)

‡	Mattison, Percy A.	Winona
†	Mienert, Albert	Winona
	Quimby, Charles W., Jr.	Winona
	Peterson, John E.	Rushford
‡	Roemer, Henry J.	Winona
‡	Rogers, Charles W.	Winona
	Satterlee, H. W.	Lewiston
†	Schmidt, Hilmar R.	Rushford
‡	Testor, James V.	Winona
‡	Tweedy, John A.	Winona
‡	Tweedy, Robert B.	Winona
	Vollmer, Frederick J.	Winona
	Wilson, Louis J.	Rushford
†‡	Wilson, R. H.	Lamoille
‡	Younger, Lewis I.	Winona

WRIGHT COUNTY MEDICAL SOCIETY

Wright County
Regular meetings, first Tuesday of the month, six times a year
Annual meeting in November
Number of members 16

PRESIDENT
Sandeen, R. M. .... Buffalo
SECRETARY
Maus, Donald J. .... Monticello

‡	Anderson, Waldo P.	Buffalo
‡	Bendix, Lester H.	Annandale
†	Catlin, John J.	Macomb, Illinois
‡	Catlin, Theodore J.	Buffalo
†‡	Ellison, Frank E.	Monticello
‡	Greenfield, William T.	Cokato
‡	Guilfoile, Pierre J.	Delano
‡	Hart, William E.	Monticello
‡	Maus, Donald J.	Monticello
‡	Purves, G. Harland	Buffalo
‡	Sandeen, Robert M.	Buffalo
	Shin, Rok	Howard Lake
‡	Smorstok, Matthew B.	Monticello
‡	Steiner, Andrew M.	St. Michael
‡	Thielen, Robert D.	St. Michael
‡	Whitesell, L. A., Jr.	Buffalo

ZUMBRO VALLEY MEDICAL SOCIETY

Olmsted, Houston, Fillmore and Dodge Counties
Regular meetings, 1st Wednesday of every odd-numbered month
Annual meeting, November
Number of members 771

PRESIDENT
Donoghue, F. Edmund .... Rochester
SECRETARY
Utz, David C. .... Rochester
EXECUTIVE SECRETARY
Fricke, Robert E. .... Rochester

‡	Aaro, Leonard A.	Rochester
†	Adler, Franz A.	Baltimore, Md.
‡	Adson, Martin A.	Rochester
‡	Affeldt, Daniel E.	Kasson
†	Ahlfs, Jacob J.	Minnetonka
†	Ahmann, David L.	Rochester
†	Aldrete, Joaquin S.	Rochester
†	Allocco, Dominic J.	Chicago, Ill.
†	Altman, Robert L.	Rochester
†	Amberg, Samuel	Rochester
†	Amos, David A.	Rochester
†	Anastasi, Lorene M.	Rochester
‡	Andersen, Howard A.	Rochester
†	Andersen, Robert L.	Rochester
#	Anderson, Dale L.	Asmara, Ethiopia, Africa
†‡	Anderson, Mark J.	Sun City, Ariz.
‡	Anderson, Markham J., Jr.	Rochester
‡	Anderson, Milton W.	Rochester
†	Andreini, Paul H.	Rochester
†	Anzalotta-Hernandez, Jose	Rochester
†	Arnold, Gordon B.	Duluth
†	Auerbach, Arthur M.	Rochester
†	Auger, Armand J.	Rochester
	Baars, Conrad W.	Rochester
†	Babb, Richard R.	Rochester
‡	Baggenstoss, Archie H.	Rochester
‡	Bair, Hugo L.	Rochester
‡	Baird, Raymond L.	Harmony
†	Baitz, Thomas	Rochester
¶	Bajec, Dusan	Poljane, Yugoslavia
‡	Baker, George S.	Rochester
†	Baker, Harry R.	Hayfield
‡	Baker, Hillier L., Jr.	Rochester
†	Baker, James A.	Rochester
	Balfour, William M.	Lawrence, Kansas
†	Banaszak, Edward F.	Rochester
‡	Banner, Edward A.	Rochester
†‡	Barker, Nelson W.	Rochester
†	Barnes, Arlie R.	Rochester
‡	Barry, Maurice J., Jr.	Rochester
‡	Bartholomew, Lloyd G.	Rochester
‡	Bastron, James A.	Rochester
	Bayrd, Edwin D.	Rochester
‡	Beabout, John W.	Rochester
‡	Beahrs, Oliver H.	Rochester
†	Beaudry, Rene'	Rochester
†	Beaumier, John H.	Rochester
†	Bechamps, Gerald J.	Rochester
†	Becton, James L.	Baltimore, Md.
‡	Belau, Paul G.	Rochester
†	Benedict, William L.	Rochester
‡	Bennett, Clayton J.	Rochester
†	Benson, William F.	Rochester
‡	Berge, Kenneth G.	Rochester
	Berkman, David S.	Emily
†‡	Berkman, John M.	Rochester
‡	Bernatz, Philip E.	Rochester
‡	Bianco, Anthony J., Jr.	Rochester
‡	Bickel, William H.	Rochester
	Bickford, Joyce A.	Rochester
†	Bigelow, Charles E.	Dodge Center
†	Birtwell, William M., Jr.	Rochester
‡	Bisel, Harry F.	Rochester

Zumbro Valley Medical Society (Continued)

‡	Black, B. Marden	Rochester
	Black, Leo F.	Rochester
	Blackburn, Charles M.	Rochester
†	Blackwell, Charles W.	Rochester
†	Blair, Thomas R.	Rochester
	Blodgett, Randolph C., Jr.	Rochester
†	Blossman, Robert C.	Rochester
†	Blouin, Yvan P.	Rochester
†	Bolton, Charles F.	Saskatoon, Canada
†	Bonebrake, Robert A.	Rochester
†	Boseker, Edward H.	Rochester
#	Botting, Arthur J.	APO San Francisco, Calif.
‡	Bowie, E. J. Walter	Rochester
‡	Boyd, David A., Jr.	Rochester
†	Braasch, William F.	Rochester
†	Brand, Frank R.	Rochester
‡	Brandenburg, Robert O.	Rochester
‡	Broadbent, James C.	Rochester
‡	Brodhun, John C.	Rochester
†	Brookler, Kenneth H.	Rochester
†‡	Brown, Alex E.	Bradenton, Florida
‡	Brown, Arnold L.	Rochester
#	Brown, Donald J.	APO San Francisco, Calif.
‡	Brown, Henry A.	Rochester
‡	Brown, Joe R.	Rochester
†‡	Brown, Philip W.	Rochester
‡	Brown, Philip W., Jr.	Rochester
‡	Brunsting, Louis A.	Tucson, Ariz.
†	Bryar, George E.	Rochester
†	Buie, Louis A.	Rochester
‡	Burbank, Mahlon K.	Rochester
‡	Burchell, Howard B.	Rochester
‡	Burgert, E. O., Jr.	Rochester
‡	Burich, Harry F.	Rochester
‡	Burke, Edmund C.	Rochester
†	Burkhart, J. MacDonald	Rochester
‡	Burton, Robert C.	Rochester
†	Buscemi, Michael F.	Rochester
‡	Butt, Hugh R.	Rochester
‡	Cain, James C.	Rochester
‡	Callahan, John A.	Rochester
‡	Campbell, Donald C.	Rochester
‡	Campbell, Malcolm K.	Rochester
‡	Carlson, Harley C.	Rochester
	Carr, David T.	Rochester
‡	Carryer, Haddon M.	Rochester
‡	Carter, Earl T.	Rochester
†	Carter, James B.	Rochester
†	Cassella, Robert R.	New Castle, Pa.
#	Cerino, Lawrence E.	Ft. Dix, N. J.
†	Cheskes, Albert	Rochester
‡	Childs, Donald S., Jr.	Rochester
‡	Christensen, Norman A.	Rochester
‡	Clagett, O. Theron	Rochester
†	Clark, Edward C.	Rochester
†	Clark, John A.	Rochester
†	Clark, Leslie W.	Manchester, Iowa
†	Clifton, Theodore A.	Hollywood, Florida
†	Coder, Donald M.	Rochester
‡	Cody, D. Thane	Rochester
‡	Colby, Malcolm Y., Jr.	Rochester
‡	Coles, Douglas T.	Rochester
†	Colligan, Paul C.	Rochester
†	Comer, Thomas P.	Rochester
‡	Connolly, Daniel C.	Rochester
‡	Cook, Edward N.	Rochester
‡	Cooper, Talbert	Rochester
‡	Corbin, Kendall B.	Rochester
†	Corcoran, James R.	Rochester
	Corrigan, Cyril J.	Rochester
‡	Coventry, Markham B.	Rochester
†	Cox, John P.	Rochester
†	Crowder, Bennett L., II	Rochester
†	Cseuz, Kalman A. J.	Rochester
†	Culligan, David E.	Rochester
‡	Culp, Clyde E.	Rochester
‡	Culp, Ormond S	Rochester
†	Cummins, Ben M.	Rochester
†	Cyrowski, Gerald A.	Rochester
‡	Dahlin, David C.	Rochester
‡	Dale, Allan J. D.	Rochester
†	Dally, Alfred D.	Madison, Wis.
‡	Daugherty, Guy W.	Rochester
†‡	Davidson, Allan D.	Rochester
†	Davidson, Harold D.	Rochester
#	Davidson, Horace B., Jr.	Washington, D. C.
†	Davis, Austin C.	Pompano Beach, Florida
‡	Davis, George D.	Rochester
‡	Dearing, William H.	Rochester
‡	Decker, David G.	Rochester
†	Dega, Francis J.	Rochester
#	De Mordaunt, Paul R.	Mt. Clemens, Mich.
	De Remee, Richard A.	Rochester
†	De Santo, Lawrence W.	Rochester
‡	Devine, Kenneth D.	Rochester
	Devloo, Robert A.	Rochester
‡	DeWeerd, James H.	Rochester
†	deWerd, Daniel L.	Rochester
	Dickson, Edgar R.	Rochester
‡	Didier, Edward P.	Rochester
‡	Diessner, Grant R.	Rochester
#	Dietrich, Robert A.	Augusta, Ga.
†	Dilley, John J.	Rochester
#	Dillman, Carl E., Jr.	Columbia, S. C.
‡	Dinapoli, Robert P.	Rochester
‡	Dines, David E.	Rochester
‡	Divertie, Matthew B.	Rochester
†	Dixon, Claude F.	Rochester
†	Dixon, George D.	Rochester
‡	Dockerty, Malcolm B.	Rochester
†	Donadio, James V., Jr.	Rochester
‡	Donoghue, Francis E.	Rochester
†	Douglas, William W.	Rochester
‡	Douglass, Bruce E.	Rochester
‡	Doyle, James R.	Rochester
†	Drips, Della G.	Rochester
†	Duffy, John C.	Rochester
‡	Du Shane, James W.	Rochester
#	Duval, David L.	FPO New York, New York
†	Duvoisin, George E.	Rochester
‡	Dyck, Peter J.	Rochester
‡	Dyer, John A.	Rochester
†	Edwards Walter G., Jr.	Rochester
†	Eichler, George R.	Rochester
†	Ekberg, Norman L.	Rochester
‡	Elkins, Earl C.	Rochester
‡	Ellis, F. Henry, Jr.	Rochester
‡	Emmett, John L.	Rochester
†	Emmons, Helen J.	Rochester
‡	Emslander, Richard F.	Rochester
‡	Engel, Andrew G.	Rochester
	Engels, Edward P.	Rochester
†	Enoch, Douglas M.	Rochester

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Zumbro Valley Medical Society (Continued)

‡	Erich, John B.	Rochester
‡	Erickson, Donald J.	Rochester
‡	Espinosa, Raul	Rochester
†‡	Eusterman, George B.	Rochester
†	Evans, William B.	Portland, Ore.
†	Evarts, Arrah B.	Rochester
‡	Faber, John E.	Rochester
†	Fabi, Robert A.	Rochester
†	Facer, George W.	Rochester
‡	Fairbairn, John F.	Rochester
†	Farrow, George M.	Rochester
‡	Faulconer, Albert, Jr.	Rochester
†	Fawcett, Kenneth J.	Rochester
†	Feinberg, Jack H.	Rochester
	Feldmann, Floyd M.	New York, N. Y.
†	Feldt, Robert H.	Rochester
†	Felsoory, Attila	Rochester
‡	Ferguson, Richard H.	Rochester
†	Fernandez, Rafael	Rochester
‡	Ferris, Deward O.	Rochester
‡	Field, Charles A.	Rochester
†‡	Figi, Frederick A.	Rochester
#	Finkelstein, Joel	Long Beach, Calif.
#	Finley, Thomas V.	Spokane, Wash.
‡	Fluegel, John O.	Rochester
†	Foley, Ralph B.	Rochester
‡	Fontana, Robert S.	Rochester
	Forth, Ronald J.	Rochester
‡	Foulk, William T., Jr.	Rochester
†	Fox, John A.	Rochester
†	Freeman, F. Julian	Rochester
‡	Frethem, Allen A.	Rochester
†	Fricke, Robert E.	Rochester
#	Friedman, Laurence L.	San Francisco, California
†	Fuller, Alen M.	Mission, Kansas
†	Furlow, William L.	Rochester
†	Gaines, Richard K.	Rochester
	Galloway, Jackson R.	Natchez, Miss.
†‡	Gambill, Carl M.	Rochester
‡	Gambill, Earl E.	Rochester
†	Gambill, Harold D.	Rochester
†	Garber, James J.	Rochester
†	Garrick, James G.	Rochester
†	Gasior, Robert M.	Rochester
†	Gasman, David H.	Rochester
#	Gasser, Richard C.	Witchita Falls, Texas
‡	Gastineau, Clifford F.	Rochester
†	Gau, Gerald T.	Rochester
‡	Gedge, Stafford W.	Rochester
#	Gelety, Joseph E.	Lackland, AFB, Texas
‡	Geraci, Joseph E.	Rochester
†	Geurkink, Nathan A.	Rochester
†	Giffin, Herbert Z.	Rochester
†	Gilbaugh, James H., Jr.	Rochester
†	Gilchrist, Ronald W., Jr.	Oklahoma City, Okla.
#	Gillis, Samuel P.	New Albany, Miss.
†	Gisvold, John J.	Rochester
	Glick, Dallas D.	Mountain Lake
†	Golden, Harvey E.	Rochester
‡	Goldstein, Norman P.	Rochester
‡	Goldston, Edgar C.	Rochester
‡	Gomez, Manuel R.	Rochester
‡	Good, C. Allen, Jr.	Rochester
	Gordon, Richard S.	Rochester
‡	Gould, Allan B., Jr.	Rochester
#	Gracey, Douglas R.	Belleville, Ill.
‡	Green, Paul A.	Rochester
#	Greenberg, Eugene	Ft. Polk, La.
†	Greene, Jerry G.	Rochester
‡	Greene, Laurence F.	Rochester
‡	Gregg, James A.	Rochester
†	Grimes, Allen E., Jr.	Rochester
†‡	Grindlay, John H.	Rochester
‡	Gross, John B.	Rochester
†	Guillory, Joel R., Jr.	Rochester
†	Gulledge, Albert D.	Rochester
†	Gurtner, Gail H.	Rochester
†	Hacker, Philip K.	Rochester
‡	Hagedorn, Albert B.	Rochester
‡	Hahn, Richard G.	Rochester
	Haidinyak, Anton L.	Rochester
†‡	Haines, Samuel F.	Rochester
†	Hall, Jack W.	Rochester
‡	Hallberg, Olav E.	Rochester
‡	Hallenbeck, George A.	Rochester
‡	Hallermann, Franz J.	Rochester
†	Hamilton, Ronald D.	Rochester
‡	Hanlon, David G.	Rochester
†	Hansen, Raymond L.	Rochester
†	Hanson, Jerome R.	Rochester
†	Hanson, Kenneth C.	Rochester
‡	Hanson, Norbert O.	Rochester
#	Hanton, Edward M.	Ft. Leonard Wood, Mo.
‡	Hargraves, Malcolm	Rochester
†	Harrington, Ryan B.	Fargo, N. D.
†	Harrington, Stuart W.	Rochester
‡	Harris, Lloyd E.	Rochester
‡	Harrison, Carlos E.	Rochester
‡	Harrison, Edgar G., Jr.	Rochester
‡	Hartfield, James E., Jr.	Rochester
	Hartridge, Virginia B.	Rochester
‡	Hayles, Alvin B.	Rochester
†	Hays, James C.	Rochester
†	Hazelrig, Cooper G.	Rochester
†	Heck, Frank J.	Wakefield, N. H.
†‡	Heidel, Werner	Rochester
†	Henderson, Darrell L.	Rochester
‡	Henderson, Edward D.	Rochester
‡	Henderson, John W.	Rochester
‡	Henderson, Lowell L.	Rochester
‡	Hepper, Norman G.	Rochester
‡	Hermans, Paul E.	Rochester
†	Hewitt, Edith S.	Rochester
†	Hewitt, Richard M.	Rochester
‡	Higgins, John A.	Rochester
†	Hightower, Billy M.	Rochester
†	Hilgers, Robert D.	St. Paul
‡	Hill, John R.	Rochester
‡	Hill, Richard W.	Rochester
	Hines, Edgar A., Jr.	Brevard, N. C.
†	Hoagland, H. Clark	Rochester
‡	Hodgson, Corrin H.	Rochester
‡	Hodgson, John R.	Rochester
‡	Hoffman, Harry N., II	Rochester
	Holbrook, Margaret A.	Rochester
	Holland, C. R.	Rochester
‡	Hollenhorst, Robert W.	Rochester
‡	Holley, Keith E.	Rochester
†	Hollowell, O. Weems	Rochester
‡	Holman, Colin B.	Rochester
†	Hood, Roderick P.	Rochester
‡	Hoover, Norman W.	Rochester
†‡	Horton, Bayard T.	Rochester
†	Houston, Hal E., Jr.	Rochester

Zumbro Valley Medical Society (Continued)

‡	Howard, Frank M., Jr.	Rochester
‡	Howell, Llewelyn P.	Rochester
†	Hudgins, Robert L.	Rochester
‡	Huizenga, Kenneth A.	Rochester
‡	Hunder, Gene G.	Rochester
‡	Hunt, Arthur B.	Rochester
‡	Hunt, James C.	Rochester
†	Hutton, Frederick A.	Rochester
†	Isbell, Robert G.	Rochester
‡	Ivins, John C.	Rochester
‡	Ivy, Horace K.	Rochester
‡	Jackman, Raymond J.	Rochester
†	Janes, Donald R.	Rochester
‡	Janes, Joseph M.	Rochester
#	Janis, John F.	Ft. Eustis, Va.
‡	Johnson, Carl E.	Rochester
#	Johnson, Dexter W.	Newllano, La.
‡	Johnson, Einer, W., Jr.	Rochester
†	Johnson, Gerhard J.	Rochester
	Johnson, Ralph B.	Lanesboro
‡	Johnson, William J.	Rochester
†	Jones, Frank E., III	Rochester
†	Jones, Harry F.	Rochester
†	Jones, H. Royden, Jr.	Rochester
*‡	Joyce, George L.	Rochester
‡	Joyce, John W.	Rochester
‡	Judd, Edward S.	Rochester
‡	Juergens, John L.	Rochester
‡	Kaese, Werner E.	Rochester
‡	Karnes, William E.	Rochester
‡	Kavanaugh, Gerald J.	Rochester
‡	Kazmier, Francis J.	Rochester
‡	Kearns, Thomas P.	Rochester
‡	Keating, F. Raymond	Rochester
‡	Keith, Haddow M.	Rochester
†	Keith, Norman M.	Rochester
†	Kelley, John J.	Rochester
‡	Kelly, Patrick J.	Rochester
‡	Kempers, Roger D.	Rochester
†	Kenefick, Thomas	Rochester
‡	Kennedy, Charles C.	Rochester
*†‡	Kennedy, Roger L. J.	Rochester
†	Kern, Eugene B.	Rochester
†‡	Kernohan, James W.	Rochester
‡	Kerr, Frederick W. L.	Rochester
	Kettering, Ronald F.	Rochester
†	Keys, Thomas F.	Rochester
‡	Kiely, Joseph M.	Rochester
‡	Kierland, Robert R.	Rochester
†	Kimber, William J.	Rochester
	Kincaid, O. W.	Rochester
†	King, John N.	Rochester
‡	Kinney, Vernard R.	Rochester
‡	Kirby, Thomas J., Jr.	Rochester
‡	Kirklin, John W.	Rochester
	Klass, Donald W.	Rochester
†	Kline, Richard J.	Rochester
‡	Knapp, Robert D., Jr.	Rochester
‡	Knutson, Lewis A.	Spring Grove
†	Koch, Michael F.	Rochester
†	Koch, Myron	Rochester
	Koelsche, Giles A.	Rochester
‡	Kottke, Bruce A.	Rochester
†	Krueger, Haven C.	Rochester
‡	Krupp, Neal E.	Rochester
†	Kubista, Theodore P.	Rochester
	Kublin, John G.	Rochester
‡	Kvale, Walter F.	Rochester
‡	Kyle, Robert A.	Rochester
†	LaHood, Joseph J.	Rochester
‡	Lake, Clifford F.	Rochester
†	Lapp, N. LeRoy	Rochester
†	Laroche, Gilles	Rochester
†	Larson, Stephen L.	Rochester
†	Laurnen, Edwin L.	Rochester
†	Lawrence, Harry M., Jr.	Rochester
‡	Lee, Raymond A.	Rochester
‡	Lee, Robert E.	Rochester
	Lehar, Thomas J.	Rochester
‡	Leonard, Paul F.	Rochester
†	Lescher, Theodore C.	Rochester
#	Levis, Michael P.	Glenshaw, Pa.
†	Lewallen, Gene S.	Rochester
†	Lewis, Andrew J.	Rochester
‡	Lillie, John C.	Rochester
#	Lindsay, Malcolm I., Jr.	Ft. McClellan, Ala.
‡	Linman, James W.	Rochester
‡	Linscheid, Ronald L.	Rochester
‡	Lipscomb, Paul R.	Rochester
‡	Litin, Edward M.	Rochester
‡	Litzow, Thaddeus J.	Rochester
‡	Lofgren, Eric P.	Rochester
‡	Lofgren, Karl A.	Rochester
‡	Logan, George B.	Rochester
†	Long, Richard J.	Rochester
†	Longo, Margaret F.	Rochester
‡	Love, J. Grafton	Rochester
†	Lufkin, Murray W.	Rochester
‡	Lundborg, Richard O.	Rochester
#	Lynch, Miles W.	Atlanta, Ga.
‡	Lynn, Hugh B.	Rochester
†	Lysak, Walter R.	Rochester
‡	McBean, James B.	Rochester
#	McCarthy, Laurence	Honolulu, Hawaii
†	McCloy, Randolph M.	Rochester
‡	McConahey, William M., Jr.	Rochester
‡	McDuffie, Frederic C.	Rochester
‡	McGill, Douglas B.	Rochester
‡	McGoon, Dwight C.	Rochester
‡	McIlrath, Donald C.	Rochester
	McKenna, Charles H.	Rochester
†	McLeod, William A.	Rochester
‡	McPherson, James R.	Rochester
#	McRoberts, Jerry W.	Bremerton, Wash.
‡	MacCarty, Collin S.	Rochester
	MacLean, Alexander R.	Winona
†	MacKenzie, Kenneth R.	Rochester
†	Macy, Norman E.	Rochester
†‡	Magath, Thomas B.	Rochester
	Magid, Gail A.	Santa Cruz, Calif.
†	Magness, John L.	Rochester
‡	Maher, Frank T.	Rochester
#	Mair, Douglas D.	Goldsboro, N. C
‡	Maldonado, Jorge E.	Rochester
‡	Malkasian, George D., Jr.	Rochester
‡	Mankin, Harold T.	Rochester
‡	Marcoux, J. Paul	Rochester
‡	Martens, Theodore G.	Rochester
‡	Martin, Gordon M.	Rochester
‡	Martin, Harold R.	Rochester
†	Martin, John H.	Rochester
‡	Martin, John T.	Rochester
‡	Martin, Maurice J.	Rochester

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Zumbro Valley Medical Society (Continued)

‡	Martin, William J.	Rochester
†	Masson, Duncan M.	Rochester
†	Masson, James C.	Rochester
‡	Masson, James K.	Rochester
†	Mastan, Peter F.	Rochester
‡	Mathieson, Don R.	Rochester
#	Mattson, Donald S.	Wonju, Korea
†	Maupin, Roger A.	Rochester
#	Maurer, Sidney, W., Jr.	Ankara, Turkey
†	May, John C.	Rochester
	Mayberry, William E.	Rochester
	Mayne, John G.	Rochester
†‡	Mayo, Charles W.	Rochester
†	Merideth, John	New York, N. Y.
‡	Merritt, Wallace A.	Rochester
†	Meyerding, Henry W.	Rochester
†	Miller, Alfred	Rochester
†	Miller, John W., Jr.	Aberdeen Prov. Grounds, Md.
‡	Miller, Roland D.	Rochester
‡	Miller, Ross, H.	Rochester
‡	Miller, W. Eugene	Rochester
	Millichap, Joseph G.	Chicago, Ill
‡	Millikan, Clark H.	Rochester
‡	Mills, Stephen D.	Rochester
†	Moeller, Henry G., IV	Rochester
†‡	Moersch, Fred P.	Fort Lauderdale, Florida
†‡	Moersch, Herman J.	Rochester
‡	Moertel, Charles G.	Rochester
‡	Moffitt, Emerson A.	Rochester
†	Mohney, Russell E., Jr.	Rochester
‡	Molnar, George D.	Rochester
†‡	Montgomery, Hamilton	Rochester
†	Moore, Gordon L., II	Rochester
	Mori, Hideo	Grand Meadow
‡	Morlock, Carl G.	Rochester
‡	Morrow, George W., Jr.	Rochester
†	Morse, Robert M.	Rochester
‡	Mulder, Donald W.	Rochester
‡	Muller, Sigfrid A.	Rochester
†	Mundy, Betty Lee	Rochester
†	Murray, James J., Jr.	Rochester
	Mussey, Mary E.	Rochester
†	Myers, George H., Jr.	Rochester
‡	Myers, Thomas T.	Rochester
†	Nadeau, Claude	Ouebec, Canada
‡	Neault, Roger W.	Rochester
	Nehring, Jesse P.	Preston
†	Nelson, Evan L., Jr.	Rochester
†	Nelson, J. Phillip	Rochester
†	Nelson, Rodger K.	Rochester
†	Newcomer, Albert D.	Rochester
‡	Nichols, Donald R.	Rochester
†	Nichols, Robert A.	Rochester
#	Nirschl, Robert P.	Jamaica, N. Y
†	Nobrega, Fred T.	Rochester
†	Nolan, Alfred C.	Rochester
	O'Connell, Edward J.	Rochester
†	O'Donnell, Kevin T.	Rochester
†	Oberstein, Barry J.	Rochester
†	Obetz, Samuel W.	Rochester
†	Odyniec, Norman	Rochester
†	Oels, Helen C.	Rochester
‡	Olsen, Arthur M.	Rochester
‡	Olson, Ernest A.	Pine Island
	Olson, Grant E.	West Concord
‡	Ongley, Patrick A.	Rochester
#	Onofrio, Burton M.	Chevy Chase, Md.
	Onsgard, L. Kenneth	Houston
†	Onstad, Gerald R.	Rochester
‡	Opitz, Joachim L.	Rochester
‡	Osmundson, Philip J.	Rochester
‡	Owen, Charles A., Jr.	Rochester
‡	Palumbo, Pasquale J.	Rochester
†	Pappas, George	Rochester
‡	Paris, Jaime	Rochester
†	Parker, Joseph C., Jr.	Rochester
‡	Parker, Robert L.	Rochester
	Parkhill, Edith M.	Rochester
‡	Parkin, Thomas W.	Rochester
#	Parsons, William R.	San Diego, Calif.
‡	Paulson, John A.	Rochester
†	Payne, Robert A.	Rochester
†	Payne, Stanley R.	Rochester
‡	Payne, W. Spencer	Rochester
#	Peacock, William F., III	Bartow, Fla.
†	Pearson, John E.	Rochester
	Pease, Gertrude L.	Rochester
†	Pedace, Francis J.	Rochester
†‡	Pemberton, John deJ	Rochester
†	Pequegnat, Edouarde P.	Rochester
‡	Perry, Harold	Rochester
#	Perry, Hugh, Jr.	A.P.O. New York, New York
‡	Peters, Gustavus A.	Rochester
	Petersen, Magnus C.	Rochester
†	Peterson, Hamlet A.	Rochester
	Peterson, Lowell F. A.	Rochester
#	Peterson, Richard A.	A.P.O., Seattle, Wash.
‡	Peyla, Thomas L.	Rochester
‡	Pilling, Loran F.	Rochester
	Pinell, (Midence), Octavio C.	Rochester
†	Pluth, James R.	Watham, Mass.
	Polley, Howard F.	Rochester
‡	Pool, T. Lloyd	Rochester
†	Potter, Myron T., II	Rochester
†	Powers, Donald W.	Rochester
‡	Pratt, Joseph H., Jr.	Rochester
‡	Priestley, James T.	Rochester
‡	Pugh, David G.	Rochester
‡	Pulec, Jack L.	Rochester
‡	Purnell, Don C.	Rochester
†	Quinones, Cesar A.	Rochester
‡	Ralston, Donald E.	Rochester
†‡	Randall, Lawrence M.	Rochester
‡	Randall, Raymond V.	Rochester
†	Rawls, William E.	Houston, Texas
†	Redfield, Nicholas P.	Rochester
†	Reed, John H., Jr.	Rochester
†	Reed, Ralph R.	Rochester
‡	Reese, David F.	Rochester
†	Reeves, Bradford F.	Rochester
‡	Reiher, Jean	Rochester
‡	Reitemeier, Richard J.	Rochester
‡	Re Mine, William H., Jr.	Rochester
‡	Restall, Charles J.	Rochester
†	Retzlaff, John A.	Rochester
†	Rheault, J. Gerald	Rochester
‡	Riggs, Byron L., Jr.	Rochester
†	Riley, Fenwick, C.	Rochester
‡	Risser, Alden F.	Stewartville
†	Robertson, Dennis M.	Rochester
‡	Rogne, William G.	Spring Grove
‡	Rome, Howard P.	Rochester

Zumbro Valley Medical Society (Continued)

‡	Rooke, Edward D.	Rochester
‡	Rosenow, Edward C., III	Rochester
‡	Rosevear, John W.	Rochester
‡	Ross, James V., Jr.	Rochester
‡	Rovelstad, Randolph A.	Rochester
†	Royals, Daggett O.	Rochester
#	Rubenstein, Mark M.	San Francisco, Calif.
‡	Rucker, Charles W.	Rochester
#	Rudis, Bernard P.	Fresno, Calif.
‡	Rushton, Joseph G.	Rochester
†	Russell, Thomas J.	Rochester
‡	Rynearson, Edward H.	Rochester
†	Sakulsky, Stephen B.	Rochester
‡	Salassa, Robert M.	Rochester
‡	Sander, Frank V., Jr.	Rochester
#	Sanders, William M.	Ashland, Ala.
‡	Sanderson, David R.	Rochester
†	Sandow, Theodore L., Jr.	Rochester
‡	Sauer, William G.	Rochester
†	Sawtell, Robert R.	Rochester
	Sayre, George P.	Rochester
‡	Scanlan, Robert L.	Rochester
‡	Scanlon, Paul W.	Rochester
‡	Schattenberg, Thomas T.	Rochester
	Schirger, Alexander	Rochester
†	Schmid, Walter C.	Rochester
†	Schnell, Roger G.	Rochester
‡	Schoenfield, Leslie J.	Stockholm, Sweden
‡	Scholz, Donald A.	Rochester
†	Schottler, Jerry L.	Rochester
†	Schreiner, Betty J.	Rochester
†	Schulze, Robert R.	Rochester
‡	Scudamore, Harold H.	Rochester
‡	Sedlack, Richard H.	Rochester
‡	Seldon, Thomas E.	Rochester
#	Senft, Robert A.	Mountain Home AFB, Idaho
‡	Sessler, Alan D.	Rochester
#	Shamblin, James R., Jr.	Tuscaloosa, Ala.
†	Sheldon, Richard S.	Rochester
‡	Sheps, Sheldon G.	Rochester
‡	Shick, Richard M.	Rochester
†	Shulkin, Edwin S.	Rochester
‡	Siekert, Robert G.	Rochester
†	Sigler, Robert M.	Rochester
†	Silverberg, Donald S.	Rochester
†	Silverman, Louis F.	Rochester
‡	Silverstein, Murray N.	Rochester
‡	Simons, John N.	Rochester
‡	Simonton, Kinsey M.	Rochester
†	Simpson, Thomas E.	Rochester
‡	Skaug, Harold M.	Chatfield
‡	Slocumb, Charles H.	Rochester
#	Smith, David E.	Washington, D. C.
†	Smith, David L.	Rochester
†	Smith, David P.	Rochester
†	Smith, Frederick L.	Rochester
†	Smith, George R.	Rochester
†	Smith, Harry L.	Rochester
‡	Smith, Lucian A.	Rochester
‡	Smith, Ralph E.	Rochester
‡	Smith, Reginald A.	Rochester
#	Smith, Robert J., Jr.	E. Petersburg, Fla.
‡	Sones, Donald A.	Rochester
‡	Soule, Edward H.	Rochester
‡	Spencer, Robert J.	Rochester
‡	Spiekerman, Ralph E.	Rochester
‡	Spittell, John A., Jr.	Rochester
‡	Sprague, Randall G.	Rochester
†	Stackhouse (Smith) Ethel M.	Rochester
†	Starkey, Thomas A.	Rochester
‡	Stauffer, Maurice H.	Rochester
#	Stauffer, Richard N.	Middletown, R. I.
†	Stecker, Raymond H.	Madison, Wis.
‡	Steinhilber, Richard M.	Rochester
†	Stenseth, Jon H.	Rochester
‡	Stewart, James R.	Rochester
‡	Stickney, J. M.	Rochester
‡	Stillwell, George K.	Rochester
‡	Stilwell, George G.	Rochester
#	Stobbe, Juergen A.	APO New York, New York
‡	Stroebel, Charles F., Jr.	Rochester
†	Strong, Cameron G.	Ann Arbor, Mich.
	Stuart, Frank A., III	Rochester
†	Suiter, Ronald D.	Rochester
‡	Sullivan, Charles R.	Rochester
	Summerskill, William H.	Rochester
‡	Svien, Hendrik J.	Rochester
‡	Swedlund, Harry A.	Rochester
‡	Symmonds, Richard E.	Rochester
‡	Taswell, Howard F.	Rochester
‡	Tauxe, Welby N.	Rochester
†	Teller, Richard M.	Rochester
†	Templeton, Mary J.	Rochester
‡	Terry, Howard R., Jr.	Santa Cruz, Calif.
	Thomas, Juergen E.	Rochester
	Thomas, Russell L.	Rochester
†	Thompson, Dennis P.	Rochester
‡	Thompson, Gershom J.	Rochester
†	Thompson, Gershom J., Jr.	Rochester
†	Thorson, Stephen C.	Vancouver, Canada
‡	Thurber, Deloran L.	Rochester
‡	Tillisch, Jan H.	Rochester
†	Tillman, Billups P.	Rochester
‡	Tinkham, Robert G.	Rochester
‡	Titus, Jack L.	Rochester
†	Todd, David W.	Rochester
	Tomori, William Y.	Rochester
#	Turner, Norman S.	Gallup, N. M.
#	Tsang, Donald	A.P.O. San Francisco, Calif.
	Tyce, Francis A.	Rochester
‡	Uihlein, Alfred	Rochester
‡	Underdahl, Laurentius O.	Rochester
‡	Utz, David C.	Rochester
	Utz, Philip H.	La Crescent
†	Van Dellen, Richard G.	Rochester
‡	Van Herik, Martin	Rochester
†	Van Wie, August E.	Rochester
‡	Vaughn, Louis D.	Rochester
†‡	Veneziale, Carlo M.	Madison, Wis.
‡	Verby, John E.	Rochester
#	Vesper, Lee J.	Wichita Falls, Texas
	Virnig, Hildegard J.	Caledonia
†	Vrabec, Donald P.	Cleveland, Ohio
‡	Wagoner, Richard D.	Rochester
†	Wahman, Robert E.	Memphis, Tenn.
†	Wakim, Khalil G.	Rochester
‡	Wallace, Robert B.	Rochester
†	Walls, Joseph T.	Rochester
†	Walsh, John H.	Rochester
†‡	Walters, Waltman	Rochester
‡	Waltz, Arthur G.	Rochester

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Zumbro Valley Medical Society (Continued)

‡	Ward, Louis E.	Rochester
†	Warner, Robert C.	Rochester
†‡	Watkins, Charles H.	Redlands, Calif.
†	Weaver, Arthur L.	Rochester
†	Webb, Donald E.	Rochester
‡	Weed, Lyle A.	Rochester
‡	Weeks, Richard E.	Rochester
‡	Weidman, William H.	Rochester
†	Weingart, Jon L.	Rochester
#	Weinman, Darrell T.	Wichita Falls, Texas
†‡	Weir, James F.	Rochester
†	Weis, Andrew J.	Rochester
‡	Welch, John S.	Rochester
†	Wellek, Mark A.	Rochester
‡	Wellman, William E.	Rochester
	Wellner, Theodore O.	Rochester
‡	Wente, Harold A.	Rochester
†	Westbrook, Philip R.	Rochester
‡	Westrup, John E.	Lanesboro
†	Wheeler, Donald K.	Rochester
‡	Whisnant, Jack P.	Rochester
#	White, William L.	San Antonio, Texas
†	Whittaker, Lorin D., Jr.	Rochester
†	Wilbur, Robert D.	Rochester
	Wilkowske, Conrad J.	Rochester
†	Williams, David Earle	Rochester
#	Williams, David Eugene	Lahore, W. Pakistan
‡	Williams, Tiffany J.	Rochester
†	Willius, Fredrick A.	Rochester
†	Wilson, David F.	Rochester
†	Wilson, M. Robert	Rochester
‡	Wilson, Paul F.	Rochester
‡	Wilson, Robert B.	Rochester
‡	Wilson, Viktor O.	Rochester
†	Wiltsie, John C.	Rochester
‡	Winkelmann, Richard K.	Rochester
‡	Witten, David M.	Rochester
‡	Wollaeger, Eric E.	Rochester
†	Wood, Lloyd T.	Rochester
†	Woods, John E.	Rochester
†	Woodworth, Hugh, Jr.	Rochester
†	Woolam, Gerald L.	Rochester
‡	Woolner, Lewis B.	Rochester
‡	Worthington, John W., Jr.	Rochester
†	Wright, Charles L., Jr.	Rochester
†	Wychulis, Adam R.	Rochester
	Wyckoff, Francis J.	Rochester
†	Wyman, John B.	Rochester
†	Yackel, Douglass B.	Rochester
†	Yalowitz, Philip A.	Rochester
‡	Yoss, Robert E.	Rochester
†	Youman, Joseph D., III	Rochester
‡	Young, Henry H.	Rochester
†	Zacharski, Leo R.	Rochester

ALPHABETIC ROSTER

Key to Symbols

# Service
* Deceased
† Life, Associate, Affiliate and Resident
¶ Honorary

A

*†	Aanes, Almer M.	Red Wing
	Aaro, Leonard A.	Rochester
	Abraham, Arden L.	Duluth
	Abrams, Alexander, Jr.	St. Paul
	Abramson, Burton I.	Minneapolis
	Abramson, Milton	Minneapolis
	Abullarade, Jose A.	Minneapolis
	Adair, Albert F., Jr.	St. Paul
	Adams, Brandon L. W.	Owatonna
	Adams, Harold R.	St. Paul
	Adams, Patrick J.	Shakopee
	Adams, Richard I.	Minneapolis
	Adcock, Leon L.	Minneapolis
	Addy, Edward R.	Gilbert
	Adkins, C. Douglas	Minneapolis
*	Adkins, Galen H.	Cambridge
	Adkins, James T.	Bertha
†	Adler, Franz A.	Baltimore, Md.
	Adson, Martin A.	Rochester
	Affeldt, Daniel E.	Kasson
	Aga, John H.	Brainerd
	Agustsson, Hreidar	Minneapolis
	Ahern, Eugene E.	Minneapolis
†	Ahlfs, Jacob J.	Minnetonka
	Ahlstrom, Robert C.	Braham
†	Ahmann, David L.	Rochester
	Ahola, Kenneth E.	Hibbing
	Ahrens, Curtis F.	Duluth
	Ahrens, Robert M.	St. Paul
	Akins, Willard M.	Red Wing
	Alari, Heino	Excelsior
	Albrecht, Raymond J.	St. Paul
	Alcorn, William J.	Wabasso
	Alden, Charles W.	Kimball
	Alden, John F.	St. Paul
†	Aldrete, Joaquin S.	Rochester
	Alexander, Harlan A.	Minneapolis
	Aling, Charles A.	Minneapolis
†	Allen, James R.	Edina
	Allen, John H.	Montevideo
	Allison, David D.	Litchfield
†	Allocco, Dominic J.	Rochester
	Alter, Milton	Minneapolis
	Altman, Robert L.	Rochester
†	Altnow, Hugo O.	Coral Gables, Florida
	Alton, Donald G.	St. Paul
	Amatuzio, Donald S.	Minneapolis
†	Amberg, Samuel	Rochester
	Amerongen, Werner W.	St. Paul
	Amick, Arthur	Worthington
†	Amos, David A.	Rochester
	Amren, Don P.	Minneapolis
†	Anastasi, Lorene M.	Rochester
	Anderegg, Alfred F.	St. Paul
	Andersen, Howard A.	Rochester
	Andersen, James G.	Minneapolis
†	Andersen, Robert L.	Rochester
	Anderson, Arden O.	Brainerd
	Anderson, Arnold S.	Minneapolis
	Anderson, Ben H.	Minneapolis
	Anderson, Chester A.	Hector
	Anderson, Chester A.	Madison
#	Anderson, Dale L.	Asmara, Ethiopia, Africa
	Anderson, David M.	Minneapolis
	Anderson, David P., Jr.	Austin
†	Anderson, Edward D.	Vaud, Switzerland
	Anderson, Ernest R.	Minneapolis
	Anderson, Frank J.	Minneapolis
	Anderson, Franklin	Owatonna
	Anderson, Harold J.	Austin
	Anderson, James J.	St. Paul
	Anderson, James M.	Duluth
	Anderson, Jo E.	LeSueur
	Anderson, John A.	Minneapolis
	Anderson, John W.	Blue Earth
	Anderson, Karl W.	Excelsior
	Anderson, Margaret C.	St. Paul
†	Anderson, Mark J.	Sun City, Ariz.
	Anderson, Markham J., Jr.	Rochester
	Anderson, Milton W.	Rochester
	Anderson, Oscar D.	Mankato
†	Anderson, Richard E.	Willmar
	Anderson, Richard W.	St. Paul
	Anderson, Richard W.	Minneapolis
	Anderson, Roger E.	Minneapolis
	Anderson, Roger L.	Minneapolis
	Anderson, Roland G.	Thief River Falls
	Anderson, Russell H.	Virginia
	Anderson, Thomas P.	Minneapolis
	Anderson, U. Schuyler	Fargo, No. Dakota
	Anderson, Waldo P.	Buffalo
	Anderson, Wallace E.	Clearbrook
	Anderson, Wallace E.	Minneapolis
	Anderson, Wallace R.	Minneapolis
†	Anderson, Werner W.	Cincinnati, Ohio
	Anderson, William H.	Minneapolis
	Anderson, William T.	Minneapolis
	Anderson, W. Robert	Minneapolis
†	Andreassen, Einar C.	Minneapolis
	Andreassen, Rolf L.	Minneapolis
†	Andreini, Paul H.	Rochester
	Andresen, Karl d'A	Minneapolis
	Ankner, Frank J.	Minneapolis
	Anonsen, Richard E.	Minneapolis
	Anselment, Lois A.	Excelsior
	Antonow, Arthur M.	Virginia
†	Anzalotta-Hernandez, Jose	Rochester
†	Arends, Archabald L.	Minneapolis
	Arey, Stuart Lane	Minneapolis
	Arhelger, Stuart W.	Minneapolis
	Arko, Frank R.	Hibbing
	Arlander, Clarence E.	Minneapolis
	Arling, Leonard S.	Minneapolis
	Arms, James J.	Minneapolis
	Armstrong, Byron H.	Minneapolis
	Armstrong, Ralph S.	Winnebago

†	Arndt, Harry W.	Detroit Lakes
	Arnesen, John F.	Owatonna
	Arnesen, Paul M.	Mankato
	Arneson, Arthur I.	Morris
	Arnold, Ann W.	Minneapolis
	Arnold, Arthur L.	Albert Lea
†	Arnold, Gordon B.	Duluth
	Arnold, Thomas B.	Minneapolis
	Arny, Frederick P.	St. Paul
	Aruguete, Alayne	Sandstone
	Aruguete, Jose	Sandstone
*†	Arvidson, Carl G.	Minneapolis
	Arzt, Philip K.	St. Paul
	Ashmore, Herbert C.	St. Paul
	Asp, Donald	Milaca
	Asta, Joseph J.	Duluth
†	Athens, Alvin G.	Santa Barbara, California
	Atmore, William G.	Duluth
	Auerbach, Arthur M.	Rochester
	Aufderheide, Arthur C.	Duluth
†	Auger, Armand J.	Rochester
	Aughenbaugh, John W.	Minneapolis
	Aulick, Ernest J.	Paynesville
	Auran, David B.	St. Paul
	Aurelius, J. Richards	St. Paul
	Ausman, Duane R.	St. Paul
	Austrian, Sol	St. Paul
	Autrey, William A.	St. Cloud
	Azad, A. M.	Minneapolis

B

	Baab, Robert O.	Crookston
	Baars, Conrad W.	Rochester
	Babb, Frank S.	St. Paul
†	Babb, Richard R.	Rochester
	Bach, Jerome M.	St. Paul
	Backus, Byron C.	Cloquet
	Backus, Lloyd B.	Cloquet
	Backus, Reno W.	Nopeming
†	Badeaux, George I.	Brainerd
	Bader, J. L.	Slayton
	Baggenstoss, Archie H.	Rochester
	Baggenstoss, Osmond J.	Minneapolis
	Bagley, Charles M.	Duluth
	Bagley, Elizabeth C.	Duluth
	Bagley, Russell W.	Minneapolis
*†	Bagley, William R.	Duluth
	Bah, Merle C.	St. Paul
	Baich, Velemir M.	Coleraine
	Bair, Hugo L.	Rochester
	Baird, Raymond L.	Harmony
†	Baitz, Thomas	Rochester
¶	Bajec, Dusan	Poljane, Yugoslavia
	Baken, Melvin P.	Minneapolis
	Baken, Melvin P., Jr.	Minneapolis
	Baker, Abe B.	Minneapolis
†	Baker, Alfred T.	Minneapolis
	Baker, C. Camak	Minneapolis
	Baker, Chilton R., Jr.	St. Paul
	Baker, George S.	Rochester
†	Baker, Harry R.	Hayfield
	Baker, Hillier L., Jr.	Rochester
†	Baker, James A.	Rochester
	Baker, Jeannette L.	Fergus Falls
	Baker, Milton E.	Minneapolis
	Baker, Norman H.	Fergus Falls
	Bakke, Arnold C.	Minneapolis
	Bakkila, Henry E.	Duluth
	Balce, Regino V.	St. Paul
	Balderson, Robert P.	Grand Rapids
	Baleisis, Peter	Minneapolis
	Balfour, William M.	Lawrence, Kansas
	Balkin, Samuel G.	Minneapolis
	Ballantine, Jerome J.	St. Cloud
	Balmer, Albert I.	Duluth
	Balogh, Charles J.	Minneapolis
†	Banaszak, Edward F.	Rochester
	Bank, Harry E.	Minneapolis
	Banner, Edward A.	Rochester
	Barber, Tracy E.	Austin
	Bardon, Richard	Duluth
	Barker, John D.	Duluth
†	Barker, Nelson W.	Rochester
†	Barnes, Arlie R.	Rochester
	Barnes, Richard E.	Aurora
	Barnett, Arthur J.	Foley
	Barnett, Joseph M.	St. Paul
	Barnett, Robert M.	Minneapolis
†	Barney, Leon A.	Duluth
	Barno, Alex	Minneapolis
	Barr, James S.	Wells
	Barr, Lowell, C.	Albert Lea
	Barr, Lowell W.	Albert Lea
	Barr, Maxwell M.	Minneapolis
	Barr, Robert N.	Minneapolis
	Barrett, Earl E.	Duluth
	Barrett, Patrick J.	Minneapolis
	Barron, Jesse J.	Minneapolis
†	Barron, Moses	Beverly Hills, California
	Barry, George J.	Minneapolis
	Barry, Maurice J., Jr.	Rochester
†	Barsness, Nellie O. N.	St. Paul
	Bartholomew, Lloyd G.	Rochester
	Bartness, John E.	Albert Lea
	Bartzen, Peter J.	Duluth
	Basinger, Harold P.	Windom
	Basinger, Homer P.	Windom
	Bastron, James A.	Rochester
	Bateman, Clarence V.	Fergus Falls
	Batdorf, B. Niles	Mankato
	Bauer, Eugene L.	St. Paul
	Bauer, Paul G.	Faribault
	Baumgartner, Florian H.	Albany
	Bayley, E. Covell	Lake City
	Bayrd, Edwin D.	Rochester
	Beabout, John W.	Rochester
	Beach, Northrop	Minneapolis
	Beahrs, Oliver H.	Rochester
	Bealka, Neil M.	Stillwater
	Bean, Charles N.	Waconia
	Beard, Archibald H., Jr.	Minneapolis
	Beaton, J. Gordon	Northfield
†	Beaudry, Rene	Rochester
†	Beaumier, John H.	Rochester
†	Bechamps, Gerald J.	Rochester
	Beck, Charles J.	North St. Paul
†	Becker, Arnetta M.	Treasure Island, Fla.

	Becker, Frederic T.	Duluth
	Beckering, Gerrit	Edgerton
	Beckering, Roland G.	Edgerton
†	Becton, James L.	Baltimore, Md.
	Beek, Harvey O.	St. Paul
	Beer, John J.	St. Paul
†	Behmler, Frederick W.	Morris
	Behr, Orlo K.	Crookston
	Beirstein, Samuel	Minneapolis
	Beiswanger, Richard H.	Minneapolis
	Belau, Paul G.	Rochester
	Belcher, Royden A.	Little Falls
	Bell, Donald C.	Minneapolis
	Bell, Harry M.	Duluth
	Bellomo, James	St. Paul
	Bellomo, John	Fairmont
	Bellville, Titus P.	Minneapolis
	Belz, Reinmar	St. Paul
	Belzer, Meyer S.	Minneapolis
	Bender, James H.	Brainerd
	Bendix, Lester H.	Annandale
†	Benedict, William L.	Rochester
	Benell, Otto E.	Virginia
	Benepe, James L.	St. Paul
	Benesh, Louis A.	Minneapolis
	Benjamin, Edwin G.	Minneapolis
	Benjamin, Harold G.	Minneapolis
	Benjamin, Richard D.	Minneapolis
	Benjamin, Robert B.	Minneapolis
	Benjamin, Walter G.	Pipestone
	Bennett, Clayton J.	Rochester
	Benson, Alfred H.	Little Falls
	Benson, William F.	Rochester
	Benthack, Elaine M.	Minneapolis
	Bentz. Herman D.	Anoka
	Bepko, Marie K. (Mrs. Puumala)	Cloquet
	Berdez, George L.	Duluth
	Berestka, Stephen J.	Minneapolis
	Berg, Arnold M.	Thief River Falls
	Berg, Clinton C.	Excelsior
†	Bergan, Otto	Clinton
	Bergan, Robert O.	Duluth
	Berge, Kenneth G.	Rochester
	Berger, Alex G.	Minneapolis
	Berger, Phil R.	St. Cloud
	Bergh, George S.	Minneapolis
	Bergh, Solveig M.	Minneapolis
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	Berglund, Eldon B.	Minneapolis
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	Bergquist, James R.	Minneapolis
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†	Berkman, John M.	Rochester
	Berkwitz, Nathaniel J.	Minneapolis
	Berman, David A.	Minneapolis
	Berman, Reuben	Minneapolis
	Bernatz, Philip E.	Rochester
	Bernier, Merrill J.	North St. Paul
	Bernstein, Irving C.	Minneapolis
	Bernstein, William C.	St. Paul
	Berris, Harold	Minneapolis
	Berry, Ronald N.	Minneapolis
	Bessesen, Alfred N.	Minneapolis
	Beuning, John B.	St. Cloud
	Bevis, William D.	Minneapolis
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	Bianco, Anthony J., Jr.	Rochester
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	Bickel, William H.	Rochester
	Bickford, Joyce A.	Rochester
	Bieter, Raymond N.	Minneapolis
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	Bigler, Earl E.	Perham
	Bigler, Ivan E.	Perham
	Bilka, Paul J.	Minneapolis
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	Billman, Herbert R.	Minneapolis
	Binder, Manuel R.	Minneapolis
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†	Birtwell, William M., Jr.	Rochester
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	Bittick, Wilbur H.	Minneapolis
	Bjornson, Robert G. B.	Wailuku, Maui, Hawaii
	Black, B. Marden	Rochester
	Black, Earl J.	White Bear Lake
	Black, Leo F.	Rochester
	Black, William A.	New Ulm
	Blackard, Clyde E.	Minneapolis
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	Blake, James A.	Hopkins
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	Blomberg, Robert D.	Minneapolis
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	Bonner, John L.	Grand Rapids
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	Boone. Ervin S.	Luverne
	Borg, Joseph F.	St. Paul
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†	Bratrude, Earl J.	Hopkins
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	Braun, Rene	Minneapolis
	Brauti, E. Fred	Corvallis, Ore.
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	Brekke, Harvey J.	Minneapolis
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	Brennan, Joseph G.	Minneapolis
	Bretzke, Carl O.	Hutchinson
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	Briggs, Thomas G.	White Bear Lake
	Brigham, Charles F., Jr.	St. Cloud
	Brill, Alice K.	Minneapolis
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	Brink, Donald M.	St. Peter
	Briones, Bienvenido R.	Hopkins
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	Brodhun, John C.	Rochester
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	Broman, Harold R., Jr.	North St. Paul
	Brooker, Warren J.	Duluth
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	Brown, Arnold L.	Rochester
	Brown, Charles T.	St. Paul
	Brown, Cyrus C.	Duluth
#	Brown, Donald J.	APO San Francisco, Calif.
	Brown, Frank T.	St. Cloud
	Brown, Glenn W.	Halstad
	Brown, Hector M.	St. Paul
	Brown, Henry A.	Rochester
	Brown, James E., Jr.	St. Paul
	Brown, James P.	St. Paul
	Brown, Joe R.	Rochester
	Brown, John H.	Minneapolis
†	Brown, John M.	Rochester
†	Brown, Philip W.	Rochester
	Brown, Philip W., Jr.	Rochester
	Brown, Russell T.	Browerville
	Brown, William D.	Minneapolis
	Brown, William D., Jr.	Minneapolis
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	Brunsting, Louis A.	Tucson, Ariz.
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	Buchstein, Harold F.	Minneapolis
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	Buckley, Joseph J.	Minneapolis
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	Bugenstein, Robert H.	Minneapolis
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	Buie, Louis A., Jr.	Minneapolis
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	Bulinski, Theodore J.	St. Paul
	Bundt, Robert E.	Minneapolis
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	Burbank, Mahlon K.	Rochester
	Burchell, Howard B.	Rochester
	Buresh, Kenneth L.	Westbrook
	Burgert, E. O., Jr.	Rochester
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	Burich, Harry F.	Rochester
	Burke, Edmund C.	Rochester
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	Burklund, Edwin C.	St. Paul
	Burlingame, David A.	St. Paul
	Burman, Richard E.	Aitkin
	Burmeister, Richard O.	St. Paul
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	Burnham, Wesley H.	Minneapolis
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	Burns, Floyd M.	Milan
†	Burns, M. A.	Milan
	Burseth, Edgar C.	Mora
	Burton, J. Richard	St. Paul
	Burton, Robert C.	Rochester
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	Bush, Robert P.	St. Paul
	Bush, Roger A.	Minnetonka
†	Busher, Herbert H.	St. Paul
	Butler, John K.	Cloquet
	Butt, Hugh R.	Rochester
*†	Butturff, Carl R.	Freeborn
†	Butzer, John A.	Mankato
	Butzer, John F.	Mankato
	Byrne, William J.	St. Paul

C

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	Cain, James H.	Alexandria
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†	Calhoun, Frank W.	Albert Lea
	Calin, S. Hartley	Minneapolis
	Callahan, John A.	Rochester
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	Cameron, John H.	Clovis, New Mexico
	Camp, Ray J.	Madison
	Campaigne, Robert J.	Duluth
	Campbell, Denis V.	Fergus Falls
	Campbell, Donald C.	Rochester
	Campbell, John C.	Albert Lea
	Campbell, Malcolm K.	Rochester
	Campbell, Orwood J.	Minneapolis
	Canine, James L.	South St. Paul
	Cant, Wilbur F.	Red Wing
†	Cantwell, William F.	International Falls
	Caplan, Leslie	Minneapolis
	Card, William H.	Minneapolis
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	Cardle, James G.	Minneapolis
	Cardle, John B.	Minneapolis
	Carey, James B., Jr.	Minneapolis
	Carey, Lewis S.	St. Paul
	Carlander, Lester W.	Minneapolis
	Carlon, Donald L.	Moorhead
	Carlson, Carl E.	Alexandria
	Carlson, Charles V.	Mound
	Carlson, Harley C.	Rochester
	Carlson, Homer J.	Pelican Rapids
	Carlson. John V.	Westbrook
	Carlson, Lawrence	Minneapolis
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	Carlson, Lloyd E.	Worthington
	Carlson, Robert G.	Anoka
	Carlson, Russel E.	Stillwater
	Carlson, Vernon J.	Moorhead
	Caron, Robert P.	Minneapolis
	Carr, David T.	Rochester
	Carr, William J.	Minneapolis
	Carroll, John J.	Winsted
	Carryer, Haddon M.	Rochester
	Carter, Donald C.	St. Cloud
	Carter, Earl T.	Rochester
†	Carter, James B.	Rochester
	Carthey, Frank J.	New Ulm
	Caspers, Carl G.	Minneapolis
†	Cassella, Robert R.	New Castle, Pa.
†	Catlin, John J.	Macomb, Ill.
	Catlin, Theodore J.	Buffalo
	Cauble, Charles F.	Minneapolis
†	Cavanor, Frank T.	Minneapolis
	Cavert, H. Mead	Minneapolis
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	Ceder, Elmer T.	Minneapolis
	Cella, Joseph A.	Minneapolis
	Ceplecha, Stanley F.	Redwood Falls
#	Cerino, Lawrence E.	San Antonio, Texas
	Cervenka, Charles F.	New Prague
	Cesnik, Robert J.	Sauk Rapids
	Chadbourn, Wayne A.	Minneapolis
	Chalgren, William S.	Mankato
	Challman, S. Allan	Minneapolis
	Chandler, William M.	Minneapolis
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	Chedister, Charles R.	Minneapolis
	Chermak, Francis G.	International Falls
	Chervenak, William A.	Minneapolis
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	Chesler, Merrill D.	Minneapolis
	Child, Sherman B.	Minneapolis
	Childs, Donald S., Jr.	Rochester
	Chisholm, Tague C.	Minneapolis
	Chou, Shelley N.	Minneapolis
	Christensen, Clarence H.	Duluth
	Christensen, Eli E.	Winona
	Christensen, Llewellyn E.	Minneapolis
	Christensen, Norman A.	Rochester
	Christenson, Carl E.	Clinton
	Christenson, Leland R.	Maple Plain
	Christian, William L.	Austin
	Christiansen, Harold A.	Jackson
	Chunn, Stanley S.	Willmar
	Church, Gerald E.	Two Harbors
	Cich, John A.	St. Paul
	Ciriacy, Edward W.	Ely
	Clagett, O. Theron	Rochester
	Clapp, Hubert D.	Crookston
†	Clark, Edward C.	Rochester
	Clark, Elizabeth A. (Mrs. Halbert)	Duluth
†	Clark, Harry B.	St. Cloud
	Clark, Henry B., Jr.	Minneapolis
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	Clark, John A.	Rochester
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	Clark, Malcolm D.	Minneapolis
	Clark, Robert S.	Minneapolis
	Clark, W. Bruce	Minneapolis
	Clarke, Dean T.	Faribault
	Clarke, John W.	Waconia
	Clay, Lyman B.	Minneapolis
	Cleaves, William D.	Sauk Centre
	Clifford, George W.	Alexandria
†	Clifton, Theodore A.	Hollywood, Florida
	Closuit, Frederick C.	Aitkin
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	Cochrane, Ray F.	Minneapolis
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	Cody, D. Thane	Rochester
	Coe, John I.	Minneapolis
	Cohen, Bernard A.	Minneapolis
	Cohen, Ephraim B.	Minneapolis
	Cohen, Henry W.	Wayzata
	Cohen, Sumner S.	Minneapolis
	Colby, Malcolm Y., Jr.	Rochester
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	Cole, James S.	Minneapolis
	Cole, Wallace H.	St. Paul
	Coleman, John B.	St. Paul
	Coles, Douglas T.	Rochester
	Coll, James J.	Duluth
†	Colligan, Paul C.	Rochester
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	Collins, Roger T.	Roseau
	Colman, Edward L.	Fergus Falls
	Colton, Roger S.	St. Paul

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	Comfort, Thomas H.	St. Paul
	Conley, Francis W.	Duluth
	Conley, Robert H.	Mankato
	Conlin, F. Dixon	Minneapolis
	Conlon, Daniel C.	Minneapolis
	Connolly, Coleman J.	St. Paul
	Connolly, Daniel C.	Rochester
	Connolly, Joseph P.	West St. Paul
†	Connor, Charles E.	St. Paul
†	Cook, C. Kenneth	St. Paul
	Cook, Edward N.	Rochester
	Coombs, Carl H.	Cass Lake
	Cooper, Charles C.	Moose Lake
	Cooper, John P.	Minneapolis
	Cooper, Robert R.	Minneapolis
	Cooper, Talbert	Rochester
	Cope, Hershel B.	Virginia
	Corbin, Kendall B.	Rochester
†	Corcoran, James R.	Rochester
†	Corniea, Albert D.	Minneapolis
	Correa, Dale H.	Minneapolis
	Corrigan, Cyril J.	Rochester
	Cortez, Daniel P.	Minneapolis
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	Cosgriff, James A., Jr.	Olivia
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	Coulter, Harold E.	Minneapolis
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	Coventry, Markham B.	Rochester
	Coventry, William D.	Duluth
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	Craig, M. Elizabeth	Minneapolis
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	Culligan, Leo C.	Minneapolis
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D

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	Davis, Luther F.	Wadena
	Davis, Michael W.	A.P.O., N.Y., N.Y.
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	Davis, William I.	Moose Lake
	Dawson, James R.	St. Paul
	Dawson, Lorin D.	Worthington
	Dawson, Walter J., Jr.	Minneapolis
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	Derauf, Donald E.	St. Paul
	Derechin, William	St. Paul

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	Dickson, Franklin H.	Proctor
	Didier, Edward P.	Rochester
	Diefenbach, Eugene J.	Minneapolis
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	Dierker, Heinrich A.	Minneapolis
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	Diessner, Grant R.	Rochester
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†	Dixon, George D.	Rochester
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	Dobler, Manfred G.	Ely
	Dobson, Mervin W.	Mankato
	Docherty, John A.	Anoka
	Dockerty, Malcolm B.	Rochester
	Docksey, John W	Willmar
	Dodds, William C.	Detroit Lakes
	Dodson, Albertus F.	Brainerd
	Doebler, Myron, I.	Mora
	Doherty, Elmer M.	New Prague
	Dokken, James H.	Windom
	Dolmage, George H.	St. Paul
	Doman, Victor W.	Lakefield
	Doms, Vernon A.	Elbow Lake
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	Donatelle, Edward P.	Minneapolis
	Donoghue, Francis E.	Rochester
	Donovan, Daniel L.	Albert Lea
	Dooley, Robert T.	St. Paul
†	Dorge, Richard i.	Minneapolis
	Dornbach, Robert A.	Minneapolis
	Dorsey, George C., Jr.	Minneapolis
	Dorsey, William E.	Minneapolis
	Doscherholmen, Alfred	Minneapolis
	Douglas, William W.	Rochester
	Douglass, Bruce E.	Rochester
	Douglass, Jesse E.	Cannon Falls
†	Doxey, Gilbert L.	Minneapolis
	Doyle, James R.	Rochester
*	Drake, Carl B.	St. Paul
	Dredge, Thomas E.	Minneapolis
	Dredge, Thomas E., Jr.	Minneapolis
	Drexler, George W.	Blue Earth
	Drill, Frederick E.	Minneapolis
	Drill, Herman E.	Hopkins
†	Drips, Della G.	Rochester
	DuBois, Julian F.	Sauk Centre
	Duff, Edwin R.	Minneapolis
	Duffell, David R.	Minneapolis
†	Duffy, John C.	Rochester
	Dummer, Donald J.	New Brighton
	Duncan, Donald A.	Minneapolis
	Duncan, James W.	Moorhead
	Dunlap, Earl H.	Minneapolis
	Dunn, Robert C.	St. Paul
	Dunstan, Paul L.	Willmar
	Dupont, Joseph A.	Excelsior
	Durkin, John L.	St. Paul
	Duryea, Marbry	Minneapolis
	Duryea, Willis M.	Minneapolis
	Duryea, Willis M., Jr.	Minneapolis
	DuShane, James W.	Rochester
†	Duthoy, E. J.	Bloomington
#	Duval, David L.	FPO New York, N. Y.
	Duvall, Arndt J., III	Minneapolis
	Duvoisin, George E.	Rochester
	Dvorak, Benjamin A.	Minneapolis
	Dwan, Paul F.	Minneapolis
	Dworsky, Samuel D.	Minneapolis
	Dwyer, John J.	Duluth
	Dyck, Peter J.	Rochester
	Dyer, John Allen	Rochester
	Dyrdal, Paul J.	St. Paul
	Dysterheft, Adolf F.	Gaylord
	Dziubinski, Emil H.	St. Cloud

E

	Earl, George A.	St. Paul
	Earl, John R.	St. Paul
	Earl, Stephan H.	Minneapolis
	Eberley, Tobe S.	Benson
	Eckdale, John E.	Marshall
	Eckman, Philip F.	Duluth
	Eckman, Philip L.	Duluth
	Eckman, Ralph J.	Duluth
	Eddy, Richard L.	Alexandria
	Eder, Walter P.	Minneapolis
	Edmondson, Hugh A., Jr.	Minneapolis
	Edwards, J. Willard	St. Paul
	Edwards, Jesse E.	St. Paul
	Edwards, Lloyd G.	St. Paul
	Edwards, Richard B.	St. Paul
	Edwards, Thomas J.	St. Paul
†	Edwards, Walter G., Jr.	Rochester
	Eelkema, Herman H.	St. Paul
	Efteland, Myles E.	Minneapolis
	Egge, Sanford G.	Albert Lea
	Eginton, Charles T.	St. Paul
†	Ehrenberg, Claude J.	Boca Raton, Fla.
	Ehrlich, S. Paul	Minneapolis
	Eich, Matthew A.	Minneapolis

	Eichelberger, Dale L.	Willmar
	Eichenlaub, John E.	Minneapolis
	Eichhorn, Edmund P., Jr.	Minneapolis
†	Eichler, George R.	Rochester
	Eide, O. A.	Hancock
	Eiden, Vera M.	Minneapolis
	Eisenman, Walter	Hibbing
	Eisenstadt, David H.	Minneapolis
	Eisenstadt, William S.	Minneapolis
	Eitel, George D.	Minneapolis
†	Ekberg, Norman Lee	Rochester
*†	Ekblad, John W.	Rock Island, Ill.
†	Ekdale, Robert A.	Palo Alto, California
	Eklund, Carl D.	Duluth
	Ekstrand, LeRoy M.	Wabasha
†	Eli, Earl W.	Minneapolis
	Elias, Frank J.	Duluth
	Elkins, Earl C.	Rochester
	Ellertson, Leonard M.	Albert Lea
	Ellinger, Albert J.	Willmar
	Ellingson, Richard B.	Minneapolis
	Elliott, Harold J.	Hayfield
	Ellis, Earl W.	Elgin
	Ellis, F. Henry, Jr.	Rochester
	Ellison, Evan S.	Minneapolis
†	Ellison, Frank E.	Monticello
	Ellwood, Paul M., Jr.	Minneapolis
	Emanuel, Karl W.	Duluth
	Emerson, Edward C.	St. Paul
	Emerson, Edwin E.	Osakis
	Emmett, John L.	Rochester
†	Emmons, Helen J.	Rochester
	Emmons, Robert W.	St. Paul
	Emond, A. J.	Farmington
	Emond, Joseph S.	Farmington
	Emond, Joseph S., Jr.	Minneapolis
	Emslander, Richard F.	Rochester
	Endress, Edward K.	St. Paul
	Engberg, Edward J.	Faribault
	Engel, Andrew G.	Rochester
	Engel, Joseph P.	Minneapolis
	Engelhart, Peter C.	Minneapolis
	Engels, Edward P.	Rochester
	Engelstad, Wendell P.	Virginia
	England, Rodney W.	St. Paul
	Englund, Elvin F.	Minneapolis
	Engstrand, Oscar J.	Minneapolis
	Engstrom, E. Duane	Minneapolis
	Engstrom, George F.	St. Peter
	Engstrom, Robert B.	Mankato
	Engwall, Richard L.	Minneapolis
†	Enoch, Douglas M.	Rochester
	Enroth, Oscar E.	St. Paul
	Eppard, Raymond M.	Cloquet
	Erich, John B.	Rochester
	Erickson, Alvin O.	Long Prairie
	Erickson, Clifford O.	Minneapolis
	Erickson, Donald J.	Rochester
	Erickson, Laurence F.	Minneapolis
	Erickson, Myron E.	Minneapolis
	Erickson, Reuben F.	Minneapolis
	Erickson, Robert L.	Rosemount
	Erickson, Vernon D.	Grand Rapids
†	Ericson, Swan	Los Angeles, California
	Erlanson, A. Cornell	St. Paul
	Ersfeld, Murray P.	St. Paul
	Esensten, Sidney	Minneapolis
	Espinosa, Raul E.	Rochester
	Estrem, Ralph L.	Fergus Falls
	Estrem, Robert D.	Fergus Falls
	Ettinger, Milton G.	Minneapolis
	Etzwiler, Donnell D.	Minneapolis
†	Eusterman, George B.	Rochester
	Eustermann, John J.	Mankato
	Evans, Edward T.	Minneapolis
	Evans, Leslie M.	Sauk Rapids
†	Evans, William B.	Portland, Ore.
†	Evarts, Arrah B.	Rochester
	Evensta, John B.	Grand Rapids
	Evison, Emerson O.	Duluth
	Ewens, George B.	Virginia

F

	Faber, John E.	Rochester
†	Fabi, Robert A.	Rochester
†	Facer, George W.	Rochester
†	Fahr, George E.	Minneapolis
	Fairbairn, John F.	Rochester
	Falk, Abraham	St. Paul
†	Fallon, Virgil T.	Minneapolis
	Falls, John L.	Red Wing
	Farber, Lawrence A.	Minneapolis
	Farkas, John V.	St. Paul
	Farley. Harrison H.	Minneapolis
†	Farrow, George M.	Rochester
	Fasbender, Herman T.	Hastings
	Faul, Bennie C.	Worthington
	Faulconer, Albert, Jr.	Rochester
	Fawcett, Arthur M.	Renville
	Fawcett, Keith R.	Duluth
†	Fawcett, Kenneth J.	Rochester
	Fedor, Robert D.	Litchfield
	Fee, John G.	St. Paul
	Feeney, John M.	Minneapolis
	Feigal, David W.	Wayzata
	Feigal, William M.	Fairmont
†	Feinberg, Jack H.	Rochester
	Feinberg, Philip	Minneapolis
	Feinberg, Samuel B.	Minneapolis
	Feinstein, Julius Y.	Minneapolis
	Felder, Davitt A.	St. Paul
	Feldmann, Floyd M.	New York, New York
†	Feldt, Robert H.	Rochester
	Felion, Arthur J.	St. Paul
	Fellows, Manley F.	Duluth
†	Felsoory, Attila	Rochester
	Fenger, Ejvind P. K.	St. Paul
	Fenske, Arnold W.	Winona
	Ferguson. John N.	St. Paul
	Ferguson, Richard H.	Rochester
	Ferguson, William C.	Walnut Grove
†	Fernandez, Rafael F.	Rochester
	Ferrell, Clarence R.	Grand Rapids
	Ferris, Deward O.	Rochester
	Fesenmaier, Otto B.	New Ulm
	Fesler, Harold H.	St. Paul
	Fetzek, Albert D.	Minneapolis

	Feuling, John C.	Duluth
	Field, Anthony H.	Savage
	Field, Charles A.	Rochester
	Field, Charles W.	Minneapolis
	Fifer, Ellen Z.	Minneapolis
	Fifer, William R.	Minneapolis
	Fifield. Malcolm M.	Duluth
†	Figi, Frederick A.	Rochester
	Filiatrault, L. J.	Coon Rapids
	Filipovich, Orest N.	Minneapolis
	Finch, J. E.	Mankato
	Fingerman, David L.	Minneapolis
	Fink, Daniel L.	St. Paul
	Fink, Leo W.	Minneapolis
	Fink, Robert J.	Minneapolis
†	Fink, Walter H.	Minneapolis
	Finkelnburg, William O.	Winona
#	Finkelstein, Joel	Long Beach, Calif.
	Finley, Paul R.	Minneapolis
#	Finley, Thomas V.	Spokane, Wash.
	Fischer, John R.	Blooming Prairie
	Fischer, Mario M.	Duluth
†	Fischer, Robert F.	St. Paul
	Fisher, Dan W.	St. Paul
	Fisher, Don H.	Minneapolis
	Fisher, Isadore I.	Minneapolis
	Fisketti, Henry	Duluth
	Fitch, Charles G.	Worthington
	Fitzsimons, William E.	Brainerd
†	Fjeldstad, C. Alford	Minneapolis
†	Flancher, Leon H.	Detroit Lakes
	Flannery, Hubert F.	St. Paul
	Fleming, Dean S.	Minneapolis
	Flentje, Dale E.	Mankato
	Fletcher, Robert H.	Chisholm
	Fliehr, Richard R.	Minneapolis
	Flinn, James B.	Redwood Falls
	Floersch, Adrian J.	Owatonna
	Flom, Reynold P.	St. Paul
	Flom, Robert S.	St. Paul
	Flora, George C.	Minneapolis
	Florence, David W.	Robbinsdale
	Florine, Martin C.	Mankato
	Flory, William D.	Minneapolis
	Fluegel, John O.	Rochester
	Flynn, Bernard F.	Hibbing
	Flynn, Louis L., Jr.	St. Paul
	Flynn, Robert A.	St. Paul
	Foderick, John W.	Hastings
	Foderick, Peter P.	Hallock
†	Fogarty, Charles W.	St. Paul
	Fogelberg, Emil J.	St. Paul
	Foker, Leslie W.	Minneapolis
*†	Foley, Frederic E. B.	St. Paul
†	Foley, Ralph B.	Rochester
	Foley, Robert R.	Minneapolis
	Folsom, Louis B.	Minneapolis
	Fontana, Robert S.	Rochester
	Forbes, Edward F.	Minneapolis
	Ford, Burton C.	Marshall
	Ford, W. Harold	Minneapolis
	Forsythe, James R.	St. Paul
	Forth, Ronald J.	Rochester
	Fortier, George M. A.	Little Falls
	Fortier, Rene G.	Mankato
	Foster, Orley W.	Minneapolis
	Foulk, William T., Jr.	Rochester
*†	Fowler, L. Haynes	Newport Beach, Calif.
	Fox, James R.	Minneapolis
†	Fox, John A.	Rochester
	Fox, LeRoy J.	St. Paul
†	Franchere, Frederick W.	Lake Crystal
	Francis, David W.	Morristown
	Frane, Donald B.	Minneapolis
	Fredericks, George M.	Minneapolis
†	Frederickson, Alice C.	Willmar
	Freeman, Charles D., Jr.	St. Paul
	Freeman, Craig W.	Minneapolis
	Freeman, Donald H.	Mankato
	Freeman, Donald W.	St. Louis Park
†	Freeman, F. Julian	Rochester
†	Freeman, John P.	Glenville
	French, Bayard T.	Hibbing
	French, Lyle A.	Minneapolis
	Frethem, Allen A.	Rochester
	Frey, Richard J.	Minneapolis
	Friberg, Joseph B.	Minneapolis
†	Fricke, Robert E.	Rochester
	Fried, Louis A.	Minneapolis
†	Friedell, Aaron	Minneapolis
	Friedell, George	Minneapolis
	Friedlieb, Oskar P.	Virginia
	Friedman, Harry S.	Minneapolis
#	Friedman, Laurence L.	A.P.O. San Francisco, Calif.
	Friedrich, Bradford E.	Red Wing
	Friend, Charles A.	Minneapolis
†	Fritsche, Albert	New Ulm
	Fritsche, Carl J.	New Ulm
	Fritsche, Theodore R.	New Ulm
	Fritz, Wallace L.	St. Paul
	Froats, Charles W.	St. Paul
	Frost, John B.	Minneapolis
	Frost, Russell H.	Fargo, N. D.
	Fruchtman, Stanley A.	Minneapolis
	Frye, Charles W.	St. Paul
	Frykman, Howard M.	Minneapolis
	Frys, Russell N.	Minneapolis
	Fuglestad, Edson V.	Minneapolis
	Fulks, Raymond W.	Minneapolis
†	Fuller, Alen M.	Mission, Kansas
†	Fuller, Alice H.	Minneapolis
	Fuller, Benjamin F.	St. Paul
	Fuller, Josiah	Duluth
	Funk, Victor K.	Hopkins
	Funke, Joyce L.	St. Paul
†	Furlow, William L.	Rochester
	Furman, L. Christine	Minneapolis
	Furr, Leo	Bird Island
	Fusaro, Ramon M.	Minneapolis

G

	Gaard, Richard C.	Robbinsdale
	Gaebe, Milton B.	Clara City
	Gaertner, Frank M. J., Jr.	St. Paul
	Gaertner, John R.	St. Paul
	Gaida, Joseph B.	St. Cloud
	Gailitis, Veronika M.	St. Paul
†	Gaines, Richard K.	Rochester
	Galbraith, Richard F.	Minneapolis
	Galejs, Aina	Minneapolis
	Gallett, Lester E.	Minneapolis

	Galligan, John J.	St. Paul
†	Galligan, Margaret Mary D.	Minneapolis
	Galloway, Jackson R.	Rochester
	Galway, Charles F.	St. Paul
†	Gambill, Carl M.	Rochester
	Gambill, Earl E.	Rochester
†	Gambill, Harold D.	Rochester
	Gamble, Elbert J.	Albert Lea
	Gamm, Edgar R.	Park Rapids
†	Gammell, John H.	Minneapolis
	Garamella, Joseph J.	Minneapolis
	Garber, George L.	Winona
†	Garber, James J.	Rochester
	Gardner, Jack K.	Fairmont
†	Gardner, Victor H.	Fairmont
	Gardner, Walter P.	St. Paul
	Garetz, Floyd K.	Minneapolis
†	Garrick, James G.	Rochester
	Garrow, Douglas M.	St. Paul
	Garske, George L.	Minneapolis
	Garten, Joseph L.	Minneapolis
	Garvey, James T.	Minneapolis
†	Gasior, Robert M.	Rochester
	Gasman, David H.	Rochester
#	Gasser, Richard C.	Wichita Falls, Texas
	Gastineau, Clifford F.	Rochester
†	Gau, Gerald T.	Rochester
	Gault, Neal L., Jr.	Minneapolis
	Gault, Sarah J.	Minneapolis
	Gaute, Svend T.	St. Paul
	Gaviser, David	Minneapolis
	Gedge, Stafford W.	Rochester
†	Gehlen, Joseph N.	St. Paul
	Geib, Marvin J.	Fargo, North Dakota
	Geiser, Peter M.	Alexandria
	Geist, Robert W.	St. Paul
#	Gelety, Joseph E.	Ft. Lauderdale, Fla.
	Geller, Joseph	Minneapolis
	George, Vane P., Jr.	LeSueur
	Geraci, Joseph E.	Rochester
	Gerend, Thomas J.	Virginia
	Gerstenkorn, George B.	Milaca
	Geurkink, Nathan A.	Rochester
	Geurs, Benjamin R.	Mankato
†	Ghostley, Mary C.	Fullerton, Calif.
	Gibbs, Edward C.	St. Paul
	Gibbs, Robert W.	Minneapolis
	Giebenhain, John N.	Minneapolis
	Giere, Joseph C.	Minneapolis
	Giere, Richard W.	Minneapolis
†	Giere, Silas W.	Benson
†	Giffin, Herbert Z.	Rochester
†	Gilbaugh, James H., Jr.	Rochester
	Gilbert, Maurice G.	Minneapolis
	Gilbertsen, A. Sigrid	Minneapolis
	Gilbertsen, Victor A.	Minneapolis
	Gilchrist, Milton R.	St. Paul
†	Gilchrist, Ronald W., Jr.	Oklahoma City, Okla.
	Gildersleeve, Robert G.	Watertown
	Gill, Theodore M.	Albert Lea
	Gilles, Paul J.	Minneapolis
	Gillespie, Delmar R.	St. Paul
	Gillespie, Malcolm G.	Duluth
#	Gillis, Samuel P.	New Albany, Miss.
	Gilman, Lloyd C.	Willmar
	Gilsdorf, Donald A.	St. Paul
	Gingold, Benjamin A.	Minneapolis
	Gislason, Paul H.	Mankato
	Gislason, Solveig T.	St. Peter
†	Gisvold, John J.	Rochester
	Gjerde, William P.	Lake City
	Glaeser, John H.	Minneapolis
	Gleason, Wallace A.	St. Paul
	Glenny, William R.	St. Paul
	Glesne, Otto N.	Northfield
	Glick, Dallas D.	Mountain Lake
	Glomstad, Gary B.	Deer River
†	Gobel, Fredarick L.	Minneapolis
	Goblirsch, Andrew P.	Sleepy Eye
	Godfrey, H. Wilson	Minneapolis
#	Goethals, Paul L.	Winter Park, Fla.
	Goetz, Frederick C.	Minneapolis
	Gokcan, Muharrem	Minneapolis
	Gokcen, Barbara W.	Minneapolis
	Gold, David	Minneapolis
	Goldberg, Isadore M.	Minneapolis
	Goldberg, Marvin E.	Minneapolis
	Goldberg, Stanley M.	Minneapolis
	Golden, Harvey E.	Rochester
	Goldfarb, Benjie L.	Minneapolis
	Goldfarb, Mace G.	Minneapolis
	Goldish, Daniel R.	Duluth
	Goldish, Robert J.	Duluth
	Goldman, Leonard W.	Minneapolis
	Goldman, Theodore I.	Minneapolis
	Goldner, Meyer Z.	Minneapolis
	Goldschmidt, Volker	Duluth
	Goldsmith, Joseph W.	St. Paul
	Goldstein, Alan L.	Hopkins
	Goldstein, Norman P.	Rochester
	Goldston, Edgar C.	Rochester
	Gomez, Manuel R.	Rochester
	Good, C. Allen, Jr.	Rochester
	Good, Gary	Minneapolis
	Good, Roy H.	Northfield
	Goodchild, William R.	Minneapolis
	Goodman, Ernest	St. Paul
	Goodnow, William H.	Duluth
	Gordon, John R.	Minneapolis
	Gordon, Philip E.	Long Lake
	Gordon, Richard S.	Rochester
	Gordon, Sewell S.	St. Louis Park
	Goswitz, John T.	Mankato
	Gould, Allan B., Jr.	Rochester
	Govrik, Kalman	St. Paul
	Gowan, Lawrence R.	Duluth
	Gowan, Lawrence R., Jr.	Duluth
#	Gracey, Douglas R.	Belleville, Ill.
*†	Graham, Archibald W.	Chisholm
	Graham, Asa B.	Faribault
	Grahek, Jack P.	Ely
	Granquist, Richard D.	Hopkins
	Grant, John C.	Sauk Centre
	Grant, Suzanne	Minneapolis
†	Gratzek, Frank R.	Anoka
†	Graves, Richard B.	Red Wing
	Gray, Royal C.	Minneapolis
	Green, Clayton R.	Excelsior
	Green, Paul A.	Rochester
	Green, Robert A.	St. Louis Park
	Greenberg, Albert J.	Minneapolis
#	Greenberg, Eugene	Ft. Polk, La.
*	Greene, Daniel E.	Warren
	Greene, Gordon	Arlington
†	Greene, Jerry G.	Rochester
	Greene, Laurence F.	Rochester
	Greene, Leonard H.	Minneapolis
	Greenfield, Irving	Minneapolis

	Greenfield, William T.	Cokato
#	Greenough, William G.	Ft. Carson, Colo.
	Gregg, James A.	Rochester
	Gregoire, Earl	Bemidji
†	Greisheimer, Esther M.	Philadelphia, Pa.
	Gretsch, Gerald A.	St. Paul
	Gridley, John W.	St. Paul
	Griffin, John W.	Bemidji
	Griffin, Patrick J.	St. Paul
	Griffin, Richard P.	Benson
	Griffin, Thomas M.	St. Paul
†	Grimes, Allen E., Jr.	Rochester
	Grimes, Burton P.	St. Peter
	Grimes, Marian	Minneapolis
	Grimes, Paul T.	Park Rapids
	Grimmell, Francis J.	Minneapolis
†	Grindlay, John H.	Rochester
	Grinley, Andrew V.	Grand Rapids
	Grinvalds, Anna O.	Cambridge
	Grismer, Jerome T.	Minneapolis
	Grohs, William H.	Duluth
	Gronquist, Y. K. J.	Cloquet
†	Gronvall, Paul R.	Hopkins
	Groschupf, Richard P.	Bemidji
†	Groschupf, Theophilus P.	Bemidji
	Grose, Frederick N.	Clarissa
	Gross, John B.	Rochester
	Grotting, John K.	Minneapolis
	Gruys, Robert I.	Wells
	Guenther, Dean E.	West St. Paul
	Guilfoile, Pierre J.	Delano
†	Guillory, Joel R., Jr.	Rochester
†	Gulledge, Albert D.	Rochester
	Gullickson, Glenn, Jr.	Minneapolis
	Gumnit, Robert J.	St. Paul
	Gunlaugson, Frederick G.	Minneapolis
†	Gurtner, Gail H.	Rochester
	Gustafson, Paul O.	Minneapolis
	Gustafson, Robert W.	Granite Falls
	Gustason, Harold T.	Minneapolis
	Gustilo, Ramon B.	Minneapolis
	Guthrie, J. Cameron	St. Paul
	Guy, Jack A.	New London

H

	Haas, Jack F.	Northfield
	Haas, John W.	Minneapolis
	Haase, Donald D.	Babbitt
	Haavik, John E.	Duluth
†	Habein, Harold C.	Palo Alto, Calif.
	Haberer, Helen R.	Stacy
	Haberle, Charles A.	Minneapolis
	Hable, Orville A.	Buffalo Lake
†	Hacker, Philip K.	Rochester
	Haes, Julius E.	St. Peter
	Haesly, Warren W.	Winona
	Hagberg, Norman L.	Montevideo
	Hagedorn, Albert B.	Rochester
	Hagen, John D.	Austin
	Hagen, Kristofer	Minneapolis
*†	Hagen, Olaf J.	Moorhead
	Hagen, Wayne S.	Minneapolis
	Haglin, John J.	Minneapolis
	Hahn, Richard G.	Rochester
	Haidinyak, Anton L.	Rochester
†	Haines, Samuel F.	Rochester
	Hakanson, Erick Y.	St. Paul
	Halbert, John J.	Duluth
	Halenbeck, Philip L.	St. Cloud
	Hall, Barnard	St. Paul
†	Hall, George M.	Rochester
	Hall, Harry B.	Minneapolis
†	Hall, Jack W.	Rochester
	Hall, Wendell H.	Minneapolis
	Hallberg, Olav Erick	Rochester
	Hallenbeck, George A.	Rochester
	Hallermann, Franz J.	Rochester
	Hallgren, Roger B.	Belle Plaine
†	Halliday, Phillip V.	Duluth
	Hallin, Roger P.	Minneapolis
†	Halloran, Walter H.	Jackson
	Halme, William B.	Wadena
	Halper, Bernard	Hibbing
	Halpern, David J.	Brewster
	Halpin, Joseph E.	Rush City
	Halverson, Donald E.	Winnebago
	Halverson, Kermit J.	Parkville
	Halverson, William G.	Madelia
	Halvorsen, Daniel K.	Owatonna
	Halvorson, David C.	Northfield
	Halvorson, James W.	Zumbrota
	Hambidge, Gove, Jr.	Minneapolis
	Hamel, Arnold L.	Minneapolis
	Hamel, Joseph I.	Minneapolis
†	Hamilton, Ronald D.	Rochester
	Hammar, Lawrence M.	Mankato
	Hammarsten, James F.	St. Paul
	Hammerstrom, Robert N.	Minneapolis
	Hammes, Ernest M.	St. Paul
	Hammes, Ernest M., Jr.	St. Paul
	Handler, Seymour	Minneapolis
	Hankerson, Robert G.	Minnesota Lake
	Hanlon, David G.	Rochester
	Hannah, Hewitt B.	Minneapolis
	Hannon, Donald W.	St. Paul
	Hanover, Ralph D.	International Falls
	Hansen, Cyrus O.	Minneapolis
†	Hansen, Erling W.	Hopkins
	Hansen, Milo L.	Little Falls
†	Hansen, Olga S.	Minneapolis
†	Hansen, Raymond L.	Rochester
	Hansen, Robert E.	Hibbing
	Hansen, Rollin M.	Minneapolis
	Hansen, Theodore M.	Albert Lea
	Hanske, Edward A.	Minneapolis
	Hanson, Ernest O.	Cloquet
	Hanson, Everett C.	New York Mills
†	Hanson, Harlow J.	Minneapolis
	Hanson, Harold B.	Minneapolis
	Hanson, Harold W.	Minneapolis
†	Hanson, Henry V.	St. Paul
†	Hanson, Jerome R.	Rochester
	Hanson, John W.	Northfield
†	Hanson, Kenneth C.	Rochester
	Hanson, Lewis	Frost
†	Hanson, Malcolm B.	Osseo
	Hanson, Mark C. L.	Minneapolis
	Hanson, Mildred S.	Minneapolis

	Hanson, Norbert O.	Rochester
	Hanson, William A. H.	Wayzata
	Hanson, William B.	Minneapolis
#	Hanton, Edward M.	Ft. Leonard Wood, Mo.
	Happe, Lawrence J.	Minneapolis
	Harbaugh, John T.	St. Cloud
	Hargraves, Malcolm M.	Rochester
	Harmon, Gaius E.	St. Paul
†	Harrington, Ryan B.	Fargo, N. D.
†	Harrington, Stuart W.	Rochester
	Harrington, Vernon A.	Duluth
	Harris, John E.	Minneapolis
	Harris, Leon D.	Minneapolis
	Harris, Lloyd E.	Rochester
	Harris, Max E.	St. Paul
	Harrison, Carlos E.	Rochester
	Harrison, Edgar G., Jr.	Rochester
	Harrison, Percy W.	Worthington
	Harrison, William C.	Minneapolis
	Hart, William E.	Monticello
	Hartfiel, William F.	St. Paul
	Hartfield, James E., Jr.	Rochester
	Hartig, Marjorie	St. Paul
	Hartig, Paul R.	Minneapolis
	Hartjen, Jason K.	Bemidji
	Hartman, Evelyn E.	Minneapolis
	Hartnagel, Grant F.	Red Wing
	Hartridge, Virginia B.	Rochester
	Hartung, Elmer H.	Claremont
	Hartwich, Roger F.	Winona
	Hartwig, John A.	Minneapolis
†	Harty, Jerome L.	Minneapolis
	Hass, Frederick M.	Minneapolis
	Hastings, Donald W.	Minneapolis
	Haugan, Norman R.	Park Rapids
	Hauge, Erling T.	Minneapolis
†	Hauge, Malvin I.	Clarkfield
	Haugen, George W.	Minneapolis
	Haugen, John A.	Minneapolis
	Hauser, Donald	Minneapolis
†	Hauser, George W.	Seattle, Washington
†	Hauser, Victor P.	St. Paul
#	Hauser, Walter H.	Columbus, Ohio
	Havel, Robert J.	Minneapolis
	Haven, Walter K.	Minneapolis
*†	Havens, Fred Z.	Rochester
†	Havens, John G. W.	Minneapolis
	Hawk, Dale J.	St. Charles
	Hawkinson, Harlan W.	St. Paul
	Hawkinson, Raymond P.	Minneapolis
	Hawley, George M. B., II	Red Wing
	Hay, Lyle J.	Minneapolis
	Hayes, Albert F.	St. Paul
	Hayles, Alvin B.	Rochester
	Hays, Albert T.	Minneapolis
†	Hays, James C.	Rochester
	Haywa, E. William	Minneapolis
†	Hazelrig, Cooper G.	Rochester
	Hazen, Richard W.	Willmar
	Head, Douglas P.	Minneapolis
†	Healy, Raymond T.	Pierz
	Hebbel, Robert	Minneapolis
†	Hebeisen, Milton B.	Chaska
†	Heck, Frank J.	Wakefield, New Hampshire
	Heck, William W.	St. Paul
	Hedemark, Homer H.	Ortonville
	Hedemark, Truman A.	Ortonville
	Hedenstrom, Charles W.	St. Paul
	Hedenstrom, Frank G.	St. Paul
	Hendenstrom, Paul H.	St. Cloud
	Hedenstrom, Philip C.	Marshall
	Hedenstrom, Richard H.	St. Paul
	Hedlund, Charles J.	St. Paul
	Hedrick, William L.	Minneapolis
	Heegaard, William G.	Alexandria
	Hegrenes, Robert L.	Farmington
	Hegstad, Thomas C.	Windom
	Heiam, William C.	Cook
	Heiberg, Olaf M.	Worthington
	Heid, James K.	Little Falls
†	Heidel, Werner	Rochester
	Heilig, William R.	St. Paul
	Heimark, John J.	Mankato
	Heinz, Ivy B.	Shakopee
	Heinzerling, Carl R.	Chaska
	Heise, Carl vR.	Winona
	Heise, Herbert vR.	Winona
	Heise, Paul vR.	Winona
	Heise, Philip vR.	Winona
	Heise, William vR.	Winona
	Heisel, John G.	Duluth
	Heller, Edgar E.	Mankato
	Helseth, Hovald K.	Fergus Falls
†	Helwig, Karl L.	Duluth
	Hempel, Dean J.	Minneapolis
†	Henderson, Darrell L.	Rochester
	Henderson, Edward D.	Rochester
	Henderson, John W.	Rochester
	Henderson, Lowell L.	Rochester
	Henderson, Terrance P.	White Bear Lake
	Hendricks, Esten J.	Verndale
†	Hengstler, William H.	St. Paul
	Henke, Wilbert J.	St. Paul
	Henrikson, Earl C.	Minneapolis
†	Henry, Clarence J.	Onamia
	Henry, James S.	St. Paul
	Henry, John C.	Owatonna
	Henry, Joseph E.	Milaca
	Henry, Kenneth G.	Owatonna
	Henry, Richard T.	Titusville, Fla.
	Henwood, Wesley C.	Virginia
	Hepper, Norman G.	Rochester
	Herber, Leo	Thief River Falls
	Herbert, Willis L.	Minneapolis
	Herman, Samuel M.	St. Paul
	Hermann, Harold W.	Minneapolis
	Hermans, Paul E.	Rochester
	Herrick, Donald W.	St. Paul
†	Hertel, Garfield E.	McAllen, Texas
	Hesla, Inman A.	Austin
	Hess, Carroll N.	Minneapolis
	Hetzler, John A.	St. Paul
†	Hewitt, Edith S.	Rochester
†	Hewitt, Richard M.	Rochester
	Hiatt, John A.	Minneapolis
	Hickok, David F.	Minneapolis
	Higdon, Donald A.	St. Cloud
	Higgins, John A.	Rochester
†	Hightower, Billy M.	Rochester
	Hildebrand, John E.	Bemidji
†	Hildebrand, Lawrence D.	Minneapolis
†	Hildebrandt, Walter C.	Minneapolis
	Hilding, Anderson C.	Duluth
	Hilgedick, William R.	Chisago City
	Hilger, Jerome A.	St. Paul
	Hilger, John R.	St. Paul
	Hilger, Laurence D.	St. Paul
	Hilgermann, George O.	Minneapolis

†	Hilgers, Robert D.	St. Paul
	Hilker, Marcus D.	St. Paul
	Hilker, Robert T.	Owatonna
	Hill, Charlotte W.	St. Paul
	Hill, Earl	Minneapolis
	Hill, Elmer M.	Minneapolis
†	Hill, Frederick E.	Riverside, California
	Hill, John R.	Rochester
	Hill, Richard W.	Rochester
	Hinckley, Robert G.	Minneapolis
	Hinderaker, Harris P.	Willmar
	Hines, Edgar A., Jr.	Brevard, N. C.
	Hiniker, Louis P.	St. Paul
	Hiniker, Peter J.	St. Peter
	Hinz, Walter E.	Willmar
†	Hirschboeck, Frank J.	Duluth
	Hirsh, Stanton A.	Crookston
	Hitchcock, Claude R.	Minneapolis
	Ho, Shu Kang	St. Paul
†	Hoagland, H. Clark	Rochester
*†	Hochfilzer, John J.	St. Paul
	Hodapp, Robert V.	Willmar
	Hodges, Kenneth V.	Minneapolis
	Hodgson, Corrin H.	Rochester
	Hodgson, Jane E.	St. Paul
	Hodgson, John R.	Rochester
	Hoeg, Dwight C.	Duluth
	Hoeper, Philip G.	Mankato
	Hoff, Herbert O.	Duluth
*	Hoffbauer, Frederick W.	Minneapolis
	Hoffert, Henry E.	Minneapolis
	Hoffman, Harry N., II	Rochester
	Hoffman, Roy A.	Minneapolis
	Hoffman, Walter Lees	Minneapolis
	Hofmann, Gerald N.	Minneapolis
	Hoganson, Donald E.	Bemidji
	Hohmann, Albert	St. Paul
†	Hoidale, Andrew D.	Tracy
	Holbrook, Margaret A.	Rochester
†	Holcomb, Joel T.	Marine-on-St. Croix
†	Holcomb, O. William	St. Paul
	Holian, Darwin K.	Albert Lea
	Holland, C. R.	Rochester
	Hollenhorst, Robert W.	Rochester
	Holley, Keith E.	Rochester
	Hollinshead, W. H.	St. Paul
†	Hollowell, O. Weems	Rochester
	Holm, Donald F.	Minneapolis
	Holm, Owen W.	Crookston
	Holman, Colin B.	Rochester
	Holmberg, Conrad J.	Minneapolis
†	Holmberg, LeRoy J.	Canby
	Holmen, Robert W.	St. Paul
	Holmstrom, Carle H.	Warren
	Holt, Glen E.	Duluth
	Holt, John E.	St. Paul
	Holten, John	Moorhead
	Holzapfel, Fred C.	Minneapolis
	Hom, Leong Y. W.	Battle Lake
	Honath, Donald H.	Owatonna
†	Hood, Roderick P.	Rochester
	Hoover, Norman W.	Rochester
	Hopkins, G. Wendell	Minneapolis
	Hopperstad, J. Jerome	Minneapolis
	Hoppes, Emerson E.	Minneapolis
	Horns, Howard L.	Minneapolis
	Horns, Norman	Minneapolis
	Horns, Richard C.	Minneapolis
†	Horton, Bayard T.	Rochester
	Hoseth, Wayne L.	Minneapolis
	Hottinger, George C.	Minneapolis
	Hottinger, Raymond C.	Janesville
†	Houkom, Bjarne	Minneapolis
	Houkom, S. Sverre	Duluth
	Houle, Rollin J.	New Brighton
	Houlton, William H.	St. Paul
†	Houston, Hal E., Jr.	Rochester
	Houts, Joseph C.	Dassel
	Hovde, Gordon W.	Lindstrom
	Hovland, Melvin L.	Minneapolis
	Hovland, Richard D.	Minneapolis
	Howard, Frank M., Jr.	Rochester
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	Howard, Robert B.	Minneapolis
	Howard, Solomon E.	Minneapolis
	Howe, Newell W.	West St. Paul
	Howell, Carter W.	Minneapolis
	Howell, Llewelyn P.	Rochester
	Hoyer, Ludolf J.	Windom
	Hoyt, C. Sherman	Minneapolis
	Hruza, William J.	Madelia
	Huber, Robert W.	St. Croix Falls, Wisconsin
*	Hudec, Elwyn R.	Echo
†	Hudgins, Robert L.	Rochester
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	Huebert, Dan W.	Hutchinson
†	Huenekens, Edgar J.	Minneapolis
	Huff, John S.	Minneapolis
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	Huffington, Herb L.	Waterville
	Hughes, Bernard J.	St. Cloud
	Hughes, Gary W.	St. Paul
	Hughes, Sidney O.	Winona
	Huizenga, Kenneth A.	Rochester
	Hultkrans, Rudolph E.	Minneapolis
	Hulteng, Donald B.	Minneapolis
	Hunder, Gene G.	Rochester
	Hunt, Arthur B.	Rochester
	Hunt, James C.	Rochester
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	Hunt, Vincent R.	Red Lake Falls
	Hunter, Murray H.	Farmington
	Hunter, Samuel W.	St. Paul
	Hurr, Maland C.	Minneapolis
	Hurwitz, Milton M.	St. Paul
	Huseby, Thomas L.	St. Paul
	Husebye, Kjeld O.	St. Paul
	Hustad, Edward G.	Minneapolis
	Hutchinson, Henry	St. Cloud
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	Hymes, Charles	Minneapolis

I

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	Ide, Arthur W., Jr.	Minneapolis
	Idstrom, Linneus G.	Minneapolis
	Indeck, Walter	Minneapolis
	Ingalls, Edgar G.	Minneapolis
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†	Isbell, Robert G.	Rochester

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	Iverson, Eleanor B.	Minneapolis
	Iverson, Rolf M.	Minneapolis
	Ivins, John C.	Rochester
	Ivy, Horace K.	Rochester

J

	Jackish, George E.	Red Wing
	Jacklin, Alexander J.	Duluth
	Jackman, Raymond J.	Rochester
	Jackson, J. Albert	Minneapolis
	Jackson, Richard L.	Minneapolis
	Jackson, William C.	St. Paul
	Jacobs, Douglas L.	Willmar
	Jacobson, Clarence	Chisholm
	Jacobson, Clifford W.	Breckenridge
	Jacobson, Ferdinand C.	Duluth
	Jacobson, Leslie W.	Minneapolis
	Jacobson, Loren J.	Minneapolis
	Jacobson, Wyman E.	St. Louis Park
	Jacott, William E.	Duluth
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	Jaffe, Manuel O.	Minneapolis
	James, Ellery M.	St. Paul
	James, John W.	St. Paul
	Janda, George W., Jr.	Minneapolis
	Janecek, James, Jr.	New Brighton
	Janecky, Allen G.	Baudette
†	Janes, Donald R.	Rochester
	Janes, Joseph M.	Rochester
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	Janssen, Martin E.	St. Paul
	Jarvis, Bruce W.	Houston, Texas
	Jarvis, Charles W.	St. Paul
	Jastram, Rupert M.	St. Paul
	Jay, Alan R.	Minneapolis
	Jefferies, William L.	St. Louis Park
	Jensen, Alvin M.	Brownton
*†	Jensen, Harry C.	Minneapolis
	Jensen, John A.	Crookston
	Jensen, Nathan K.	Minneapolis
	Jensen, Paul A.	Minneapolis
	Jensen, Reynold A.	Hopkins
†	Jensen, Thorvold J.	Duluth
	Jensen, James E.	Stillwater
	Jepson, William W.	Minneapolis
	Jerome, Bourne	Minneapolis
	Jerome, Elizabeth B. K.	Minneapolis
	Jeronimus, Henry J.	Duluth
	Jessico, Charles M.	Duluth
	Jeub, Robert P.	Minneapolis
*	Joffe, Harold H.	Virginia
	Johanson, Waldemar G.	St. Paul
	John, Byron L.	St. Cloud
	Johnson, Alan R.	Windom
	Johnson, Aldridge F.	St. Paul
	Johnson, Angelo G.	Minneapolis
	Johnson, Arthur B.	Minneapolis
	Johnson, Arthur G., Jr.	Fergus Falls
	Johnson, Calvin J.	Grand Rapids
	Johnson, Carl Edwin	St. Paul
	Johnson, Carl Eric	Rochester
	Johnson, Carolyn A.	St. Paul
	Johnson, C. Percy	Tyler
	Johnson, Curtis M.	Winona
	Johnson, Daniel A.	Litchfield
	Johnson, David R.	Minneapolis
#	Johnson, Dexter W.	Newllano, La.
	Johnson, Donald A.	Minneapolis
	Johnson, Douglas L.	Little Falls
	Johnson, Edward A.	Minneapolis
†	Johnson, Einer W.	Bemidji
	Johnson, Einer W., Jr.	Rochester
	Johnson, Frank E.	Minneapolis
	Johnson, Franklin L.	Duluth
†	Johnson, Gerhard J.	Rochester
	Johnson, Gordon E.	Minneapolis
	Johnson, Herbert W.	St. Paul
†	Johnson, James A.	Minneapolis
	Johnson, John W.	Minneapolis
	Johnson, Karl E.	Duluth
	Johnson, Malcolm R.	Minneapolis
	Johnson, Marvin W.	Dassel
	Johnson, Norman P.	Minneapolis
	Johnson, Norman Paul	St. Paul
	Johnson, Norton T.	Minneapolis
	Johnson, O. Guy	Bayport
	Johnson, Olga H.	Moorhead
	Johnson, Ralph B.	Lanesboro
	Johnson, Reinald G.	Minneapolis
†	Johnson, Reuben A.	Minneapolis
	Johnson, Rex R.	New Ulm
	Johnson, Richard J.	St. Paul
	Johnson, Richard S.	Minneapolis
	Johnson, Robert E.	Minneapolis
	Johnson, Robert H.	Bayport
	Johnson, Theodore	Duluth
	Johnson, Thomas E.	St. Paul
	Johnson, Thomas H., Jr.	Minneapolis
	Johnson, Vilhelm M.	Dawson
	Johnson, William J.	Rochester
	Johnson, Youbert T.	Minneapolis
	Johnsrud, Luverne	Hibbing
	Johnston, Donald K.	Minneapolis
	Johnston, H. Wayne	Virginia
	Johnston, Leonard F.	Winona
	Jones, David G.	Minneapolis
†	Jones, Frank E., III	Rochester
†	Jones, H. Royden, Jr.	Rochester
†	Jones, Harry F.	Rochester
†	Jones, Herbert W., Jr.	Minneapolis
	Jones, Orville H.	Mankato
	Jones, Richard H.	Minneapolis
†	Jones, Richard N.	St. Cloud
	Jordan, Donald V.	Minneapolis
†	Jordan, Kathleen B. Smith	Granite Falls
*	Jordan, Lewis S.	Granite Falls
	Jorgensen, Harlan	Minneapolis
†	Jorgenson, Edward O.	Rochester
	Joseph, Arnold H.	St. Paul
*	Joyce George L.	Rochester
	Joyce, John W.	Rochester
	Judd, Allen S.	Minneapolis
	Judd, Edward S.	Rochester
	Judd, Walter H.	Washington, D. C.
†	Juergens, Herman M.	Belle Plaine
	Juergens, John L	Rochester

	Juergens, Manley F.	Stillwater
	Juers, Edward H.	Red Wing
†	Juliar, Richard O.	Los Angeles, California
	Juntunen, Roy R.	Duluth
	Jurdy, Mitchell	Minneapolis
	Just, Herman J.	Hastings

K

*†	Kaasa, Lawrence J.	Albert Lea
†	Kabrick, Ola A.	Hull, Illinois
	Kadesky, Harold B.	Minneapolis
	Kaese, Werner E.	Rochester
	Kaiser, Harold B.	Minneapolis
	Kaiser, Milton L.	New Ulm
	Kalb, Thomas J.	Minneapolis
	Kallestad, Leonard L.	Wayzata
	Kane, Dennis J.	St. Paul
	Kane, William J.	Minneapolis
	Kanne, Earl R.	Brainerd
	Kantar, Bruce L.	Minneapolis
	Kaplan, David H.	Minneapolis
	Kaplan, Harold A.	Minneapolis
	Kaplan, J. Jacob	Minneapolis
#	Kapsner, Adrian L.	Ogallala, Nebraska
	Kapsner, Alfred T.	Princeton
	Karges, Laurel E.	Grand Rapids
	Karish, Louis J.	Grand Rapids
	Karleen, Conrad I.	Minneapolis
	Karlen, Markle	Minneapolis
	Karn, Jacob F.	Ortonville
	Karnes, William E.	Rochester
	Karon, Everett H.	St. Paul
	Karon, Irvine M.	St. Paul
	Kasper, Eugene M.	St. Paul
	Kasper, Robert E.	Minneapolis
	Kath, Reinhard H.	Arlington
	Katkov, Harold	Wayzata
	Katz, Beni	Minneapolis
	Katz, Louis J.	Long Beach, California
	Kaufman, Edward J.	Appleton
†	Kaufman, William C.	Appleton
	Kavanaugh, Gerald J.	Rochester
	Kazmier, Francis J.	Rochester
	Kearney, R. Wynn	Mankato
	Kearns, Thomas P.	Rochester
	Keating, F. Raymond	Rochester
	Keil, Marcus A.	Albert Lea
	Keith, Haddow M.	Rochester
†	Keith, Norman M.	Rochester
	Keith, Paul J.	Milaca
	Keithahn, Elmer E.	Sleepy Eye
	Kelby, Gjert M.	Minneapolis
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	Kelley, Roger E.	Crosby
	Kelly, Albert C.	St. Paul
	Kelly, Charles F.	Minneapolis
	Kelly, Edward H.	St. Paul
	Kelly, Helen M.	St. Paul
	Kelly, James H.	St. Cloud
	Kelly, John C.	Minneapolis
	Kelly, John F.	Cold Spring
	Kelly, John P.	Minneapolis
	Kelly, John T.	Minneapolis
	Kelly, Joseph R.	St. Paul
	Kelly, Patrick J.	Rochester
	Kelly, Robert T.	Grand Rapids
†	Kelsey, Charleton G.	St. Paul
	Kelsey, Chauncey M.	St. Paul
†	Kemp, Alphonse F.	Mankato
	Kempers, Roger D.	Rochester
	Kenefick, Emmett V.	St. Paul
†	Kenefick, Thomas P.	Rochester
	Kennedy, Byrl J.	Minneapolis
	Kennedy, Charles C.	Rochester
†	Kennedy, Claude C.	Minneapolis
	Kennedy, George L.	Faribault
*†	Kennedy, Roger L. J.	Rochester
	Kennedy, William R.	Minneapolis
	Kenyon, Thomas J.	St. Paul
	Kerkhof, Arthur C.	Minneapolis
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†	Kernohan, James W.	Rochester
	Kerr, Frederick W. L.	Rochester
†	Kesting, Herman	St. Paul
	Kettering, Ronald F.	Rochester
	Kevern, Jay L.	Henning
†	Keyes, John D.	Winona
	Keyes, Robert W.	Pipestone
†	Keys, Thomas F.	Rochester
	Kiely, Joseph M.	Rochester
	Kierland, Robert R.	Rochester
	Kiesler, Frank, Jr.	Grand Rapids
	Kilbride, Edwin A.	Worthington
#	Kilen, Mark J.	Duluth
	Kim, Mark K.	Minneapolis
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	Kimmel, George C.	Minneapolis
	Kincaid, O. W.	Rochester
	King, Frances W.	Hopkins
†	King, John N.	Rochester
	Kinkade, Byron R.	Ada
	Kinney, Vernard R.	Rochester
†	Kinsella, Thomas J.	Minneapolis
	Kiolbasa, Edward B.	Stillwater
	Kippen, Neil	Breckenridge
	Kirby, Thomas J., Jr.	Rochester
	Kirklin, John W.	Rochester
	Kitchen, Clyde K.	Minneapolis
	Kitzberger, Peter J.	New Ulm
	Kjos, Ronald K.	Anoka
	Klass, Ronald W.	Rochester
	Klefstad, Lloyd H.	Greenbush
†	Klein, Harry	Duluth
	Klein, William A.	Duluth
	Kleinsasser, Warren L.	Farmington
†	Kline, Richard J.	Rochester
	Knapp, James F.	Detroit Lakes
	Knapp, Miland E.	Minneapolis
	Knapp, Robert D., Jr.	Rochester
†	Knight, Ralph T.	Minneapolis
†	Knight, Ray R.	Minneapolis
	Knip, Robert J.	Ortonville
	Knipp, William J.	Brainerd
	Knobloch, William H.	Minneapolis
	Knoche, Harvey A.	Gaylord
	Knoedler, John P.	Duluth
	Knoll, W. V.	Brainerd
	Knudsen, Helen L.	Minneapolis

	Knudson, Gerhard E.	St. Paul
	Knudson, Lewis A.	Spring Grove
	Knutson, Robert C.	St. Paul
†	Koch, Michael F.	Rochester
†	Koch, Myron	Rochester
	Kodres, Nina	St. Paul
	Koenig, Robert P.	St. Cloud
	Koelsche, Giles A.	Rochester
	Kohlbry, Carl O.	Duluth
	Kohlhase, Robert E.	Minneapolis
	Kolars, Charles P.	Minneapolis
	Kolars, James J.	Faribault
†	Koller, Herman M.	Minneapolis
†	Koller, Louis R.	Minneapolis
	Koller, Robert L.	Minneapolis
	Kolp, Berton A.	Glenwood
	Kooda, Jennings C.	Morris
	Koons, William R.	Mahnomen
	Korchik, John P.	Minneapolis
	Korda, Henry A.	Pelican Rapids
	Kosiak, Michael	St. Paul
	Kosiak, William	Two Harbors
	Kostick, William R.	Fertile
	Kotchevar, Frank R.	Minneapolis
	Kottke, Bruce A.	Rochester
	Kottke, Frederic J.	Minneapolis
	Kotval, Russell J.	Pipestone
	Koucky, Rudolph W.	Minneapolis
	Koutsky, Carl D.	Minneapolis
	Kozak, Michael J.	Minneapolis
	Koza, Donald W.	St. Paul
	Kozel, William J.	Morris
	Kraatz, Robert W.	St. Paul
	Kraemer, George N.	Fairmont
	Krafft, Walter E.	Minneapolis
	Kragh, Lyle V.	Minneapolis
	Kramer, James D.	St. Paul
	Krause, Carl W.	Fairmont
	Kremen, Arnold J.	Minneapolis
	Kremer, Jerome L.	Montevideo
†	Kreuzer, Titus C.	Fort Snelling
	Krezowski, Thomas K.	St. Paul
	Krieser, Albert E.	Minneapolis
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	Krueger, Victor R.	Nopeming
	Kruger, Elmer L., Jr.	Nashwauk
	Krupp, Neal E.	Rochester
	Krystosek, Lee A.	Minneapolis
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†	Kublin, John G.	Rochester
	Kucera, Frank J.	Hopkins
†	Kucera, Stanley T.	Northfield
†	Kucera, William J.	Santa Barbara, California
	Kugler, Alex A.	St. Paul
	Kuhlmann, Lawrence B.	Melrose
	Kuhlmann, Vernon G.	Alexandria
	Kulstad, Oscar S.	Dodge Center
	Kulzer, Norbert J.	Hastings
	Kump, Warren L.	Minneapolis
	Kundel, Donald W.	Duluth
	Kuske, Albert W.	St. Paul
†	Kusske, Arthur L.	New Ulm
	Kusske, Bradley W.	St. Paul
	Kusske, Douglas R.	St. Paul
	Kusz, Clarence V.	Minneapolis
	Kuz, Eugene L.	Savage
	Kvale, James N.	Atwater
	Kvale, Walter F.	Rochester
†	Kvam, Lowell L.	St. Paul
	Kvistberg, Gerald K.	St. Cloud
	Kyle, Robert A.	Rochester

L

	L'Abbe, A. J. Philip	Duluth
	LaBree, John W.	St. Louis Park
	LaBree, Robert H.	Duluth
	Lade, Roswith I.	St. Paul
	LaFond, Edward M.	St. Cloud
	Lagaard, Sheldon M.	Minneapolis
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	Laikola, Leslie A.	Adrian
†	Lajoie, John M.	Minneapolis
	Lake, Clifford F.	Rochester
	Lamb, H. Douglas	Minneapolis
	Lane, Miles I.	White Bear Lake
	Lang, Leonard A.	Minneapolis
	Langer, Leonard O., Jr.	Minneapolis
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	Lannin, Bernard G.	St. Paul
	Lannin, Donald R.	St. Paul
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†	Laroche, Gilles	Rochester
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	Larsen, Frank Wm.	Minneapolis
	Larsen, Russell H.	Lakefield
	Larson, Arnold	Detroit Lakes
	Larson, Arthur K.	Minneapolis
	Larson, Donald M.	Minneapolis
	Larson, Donald M.	Duluth
	Larson, Dorette W.	Fergus Falls
	Larson, Ernest J., Jr.	Minneapolis
	Larson, Eva Jane O.	St. Paul
	Larson, F. Wilmer	Minneapolis
	Larson, Gerald E.	Cambridge
	Larson, Keith D.	Moose Lake
	Larson, Kenneth R.	Moose Lake
	Larson, Lawrence M.	Minneapolis
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	Larson, Leland J.	Minneapolis
	Larson, Leonard M.	Minnetonka
	Larson, Leroy J.	Bagley
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	Larson, Milo H.	St. Peter
	Larson, Oliver E. H.	Zumbrota
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	Larson, Roger C.	Minneapolis
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	Larson, Wyllis G.	Minneapolis
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	Latts, Elliot M.	Minneapolis
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	Lawler, Kevin M.	St. Paul
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	Lawrow, John W.	Minneapolis
	Lawson, Warren R.	Minneapolis
	Lawton, James J., Jr.	Minneapolis
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	Lee, Norman J.	Tracy
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	Lee, Robert E.	Rochester
	Lee, William C.	Hibbing
	Leek, Joseph H.	Duluth
	Leemhuis, Andrew J.	Minneapolis
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	Lehar, Thomas J.	Rochester
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	Leitch, Cecil M.	Litchfield
	Lenander, Mellvin E. L.	St. Peter
	Lenarz, Albert J.	St. Cloud
	Lende, Norman	Faribault
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	Lenz, Joseph R.	Morton
	Lenz, Oa	Minneapolis
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	Leonard, Samuel	Minneapolis
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†	Lepak, John A.	St. Paul
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	Leppo, N. Erkki A.	Duluth
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	Leslie, W. Robert	Minneapolis
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	Lester, Malcolm J., Jr.	Truman
	Lester, Theodore H.	Minneapolis
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	Leverenz, Carleton W.	St. Paul
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	Lewis, Charles W.	Henning
	Lewis, Glenn M., Jr.	St. Paul
	Lewis, Joyce S., Jr.	St. Paul
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	Lick, William J.	St. Paul
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	Lindberg, Winston R.	Minneapolis
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	Linquist, Richard H.	Minneapolis
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	Malkasian, George D., Jr.	Rochester
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	Mann, George A.	Minneapolis
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	Marcoux, J. Paul	Rochester
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	Mark, Merle S.	Minneapolis
	Marking, George H.	Minneapolis
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	Markovitz, Jack M.	Minneapolis
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	Marso, John L.	Mankato
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	Martin, Albert C.	Luverne
	Martin, David E., III	Wabasha
	Martin, Doreen A.	Pepin, Wisconsin
	Martin, Dwight D.	St. Paul
	Martin, Frank E.	Minneapolis
	Martin, George B.	Thief River Falls
	Martin, George R.	Minneapolis
	Martin, Gordon M.	Rochester
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	Martin, Maurice J.	Rochester
	Martin, Webster C.	Duluth
	Martin, William J.	Rochester
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	Martinson, Carl J.	Wayzata
	Martinson, Elmer J.	Wayzata
	Martinson, Raymond M.	Virginia
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	Massee, Joseph S.	Minneapolis
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	Masson, James K.	Rochester
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	Mathers, John E.	Austin
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	Mathieson, Don R.	Rochester
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	Mattson, Albert D	St. James
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	Meller, Robert L.	Minneapolis
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	Menold, William F.	St. Paul
	Mensheha, Nicholas M.	Minneapolis
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	Nichols, Donald R.	Rochester
†	Nichols, Robert A.	Rochester
	Nichols, Thomas O.	St. Paul
	Nicholson, Richard W.	Fergus Falls
	Nickerson, John R.	Fairmont
	Nickerson, Neil D.	Fairmont
	Nicolay, William R.	Red Wing
	Nielsen, David J.	Minneapolis
	Nietfeld, Aloys B.	Sauk Centre
	Nilsen, John A.	Minneapolis
	Nimlos, Kenneth O.	St. Paul
†	Nimlos, Lenore O.	St. Paul
	Ninneman, Newton N.	St. Paul
#	Nirschl, Robert P.	Jamaica, N. Y.
	Nisius, George F.	Duluth
	Nisswandt, Albert L.	Duluth
	Nixon, James B.	Crosby
†	Nobrega, Fred T.	Rochester
†	Nolan, Alfred C.	Rochester
	Nolan, Robert K.	Minneapolis
	Nolen, William A.	Litchfield
	Nollet, Donald J.	Hibbing
	Noran, Harold H.	Minneapolis
†	Norberg, Carl E.	Los Altos, Calif.
	Nord, Robert E.	Minneapolis
†	Nordin, Gustaf T.	Honolulu, Hawaii
†	Nordland, Martin	Minneapolis
*	Nordland, Martin A.	Minneapolis
	Nordlund, Mildred E.	Carmichael, Calif.
	Nordman, Willard F.	Mora
	Noren, George R.	Minneapolis
	Norman, David D.	St. Paul
	Norman, Franklin C.	Minneapolis
	Norman, Mark L., Jr.	Minneapolis
	Normann, Stephen T.	Waseca
	Norval, Mildred A.	Minneapolis
*†	Novak, Edward E.	New Prague
	Nuebel, Charles J.	Long Beach, California
†	Nuessle, Walter G.	Springfield
	Nuessle, William F.	St. Louis Park
	Nuetzman, Arthur W.	Faribault
	Nydahl, Bruce C.	Minneapolis
	Nydahl, Malvin J.	Minneapolis
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	Nye, Lillian L.	St. Paul
	Nygren, William T.	Braham
	Nywall, Dean D.	Slayton

O

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	O'Brien, John C.	St. Paul
	O'Brien, Louis T.	Breckenridge
	O'Brien, William A.	Minneapolis
	O'Connell, Edward J.	Rochester
†	O'Donnell, James E.	Minneapolis
†	O'Donnell, Kevin T.	Rochester
	O'Kane, Thomas W.	St. Paul
	O'Keefe, James P.	St. Cloud
	O'Leary, John B.	Brainerd
	O'Malley, Valentine	St. Paul
	O'Neill, John C.	Duluth
	O'Neill, Nial C.	St. Paul
	O'Phelan, E. Harvey	Minneapolis
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	Ockuly, Orville E.	St. Paul
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	Odland, Mark E.	Detroit Lakes

	Odland, Olin M.	Granite Falls
†	Odyniec, Norman	Rochester
	Oeljen, Siegfried C.	Waseca
†	Oeis, Helen C.	Rochester
	Officer, Charles D.	Savage
†	Ogden, Warner	St. Paul
†	Ohage, Justus	St. Paul
	Ohmann, Ronald	Glencoe
	Olavs, Olga	Minneapolis
	Olds, George H.	New Richland
	Olfelt, Paul C.	Minneapolis
	Olinger, John N.	St. Cloud
	Olive, John T., Jr.	Mankato
	Oliver, Irwin L.	Graceville
	Olmanson, Edmund G.	St. Peter
	Olmanson, M. Donald	St. Peter
	Olmanson, Vern C.	St. Peter
	Olsen, Arthur M.	Rochester
	Olsen, E. George	Minneapolis
	Olsen, Jay R.	Minneapolis
	Olsen, Ralph L.	St. Paul
	Olson, Albert J.	Owatonna
	Olson, Alton C.	Minneapolis
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	Olson, Barbara F.	South St. Paul
	Olson, C. Kent	Minneapolis
	Olson, Carl J.	Minneapolis
	Olson, Detlof M.	Minneapolis
	Olson, Duane C.	Minneapolis
	Olson, Ernest A.	Pine Island
	Olson, Frances P.	Fergus Falls
	Olson, Grant E.	West Concord
	Olson, Gregory M.	Litchfield
	Olson, Hardin E.	Minneapolis
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	Olson, Philip A.	Minneapolis
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	Olson, Rolland A.	Wayzata
	Olson, Robert T.	Canby
	Olson, Robert W.	Minneapolis
	Ongley, Patrick A.	Rochester
#	Onofrio, Burton M.	FPO New York, N. Y.
	Onsgard, L. Kenneth	Houston
†	Onstad, Gerald R.	Rochester
	Opheim, Richard H.	Minneapolis
	Opitz, Joachim L.	Rochester
	Oppegaard, C. L.	Crookston
	Oppen, E. Gerhard	Minneapolis
	Oppen, Melvin G.	Wayzata
	Opsahl, Lawrence J.	Willmar
	Opstad, Earl T.	Minneapolis
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	Orbuch, Martin W.	Minneapolis
	Orkin, Milton	Minneapolis
	Orn, Duane L.	Minneapolis
	Orr, Burton A.	Faribault
	Osekowsky, Henry J.	St. Paul
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	Ostergaard, Erling	Elbow Lake
†	Ostergren, Edward W.	St. Paul
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	Ourada, Anthony L.	Fairmont
	Overby, Philip G.	Minneapolis
	Overland, Arnold J.	Rolla, N. D.
	Owen, Charles A., Jr.	Rochester
	Owen, Richard R.	Minneapolis
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	Owens, Frederick M.	St. Paul
	Owens, William A.	Montevideo

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	Page, Raymond L.	Minneapolis
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	Palm, Neil M.	St. Paul
	Palmer, Clinton F.	Albert Lea
	Palmer, Harry A.	Blackduck
	Palumbo, Pasquale J.	Rochester
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	Papermaster, Theodore C.	Minneapolis
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	Paris, Jaime	Rochester
	Park, Wilford E.	Minneapolis
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	Parker, Warren E.	Sebeka
	Parker, Wilbert H.	Chisholm
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	Parsons, Ralph L.	Trimont
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	Patch, Orien B.	Duluth
	Pattee, James J.	Minneapolis
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	Patterson, Hugh D.	Slayton
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	Paule, William J.	Minneapolis
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†	Payne, Stanley R.	Rochester
	Payne, W. Spencer	Rochester
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†	Pearson, John E.	Rochester

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	Penn, George E.	Mankato
	Peper, Martin C.	Minneapolis
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	Perlman, Everett C.	Minneapolis
	Perlman, Herschel L.	Minneapolis
	Perpich, Irene Kosiak	Virginia
	Perry, Harold O.	Rochester
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	Perry, John F., Jr.	St. Paul
	Person, Duane F.	Virginia
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	Petersen, Bryon D.	Minneapolis
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	Petersen, Donald H.	Willmar
	Petersen, Glenn L.	Minneapolis
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	Petersen, Robert T.	St. Cloud
	Petersen, William E.	Minneapolis
	Peterson, Charles A.	Minneapolis
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	Peterson, Donald H.	St. Paul
	Peterson, Edward A.	St. Paul
	Peterson, Edward N.	Virginia
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	Peterson, John A.	St. Paul
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	Peterson, John O.	Hastings
	Peterson, John R.	Rushford
	Peterson, Kenneth A.	Marshall
	Peterson, Kenneth H.	Hutchinson
	Peterson, Lowell F. A.	Rochester
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	Peterson, Palmer A.	Minneapolis
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	Peterson, Willard E.	Willmar
	Peterson, Willard H.	Minneapolis
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	Pettersen, George R.	Aitkin
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	Phelps, Robert D.	Minneapolis
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	Phillips, Leonard	St. Paul
	Philp, David R.	Watertown
	Pierce, Robert B.	Mountain Lake
	Pierson, Roy F.	Slayton
	Pilling, Loran F.	Rochester
	Pincus, Mitchell	Minneapolis
	Pinell, (Midence) Octavio C.	Rochester
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	Pistulka, Rolland D.	Chaska
	Plasha, Matthew K.	Coon Rapids
	Plass, Herbert F. R.	Minneapolis
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	Plucker, Milton W.	Worthington
†	Pluth, James R.	Watham, Mass.
	Pohl, John F.	Minneapolis
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	Polesky, Herbert F.	Minneapolis
	Poley, Brooks J.	Minneapolis
	Pollak, Kurt	Minneapolis
	Pollard, William S.	Duluth
	Polley, Howard F.	Rochester
	Pollock, Anthony J.	Minneapolis
	Polski, Paul G.	South St. Paul
	Polzak, Jacob A.	Minneapolis
	Pone, John J.	Minneapolis
	Ponterio, James E.	Shakopee
	Pool, T. Lloyd	Rochester
	Popadiuk, Peter	Minneapolis
	Popoff, Russel G.	Graceville
	Popovich, Dragojla	Milwaukee, Wisconsin
#	Popowich, John G.	Minneapolis
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	Poppie, Robert W.	Brainerd
†	Porter, Oliver M.	Minneapolis
	Post, Edmund A.	St. Paul
†	Potter, Myron T., II	Rochester
	Potter, Robert B.	Minneapolis
	Power, John E.	Duluth
†	Powers, Donald W.	Rochester
	Powers, Robert L.	St. Paul
†	Pratt, Fred J., Sr.	Minneapolis
	Pratt, Fred J., Jr.	Minneapolis
	Pratt, Joseph H., Jr.	Rochester
†	Prentice, Walter B.	St. Paul
	Prem, Konald A.	Minneapolis
	Preston, Frank S., Jr.	Minneapolis
	Price, William E.	Minneapolis
	Prickman, William E.	Minneapolis
	Priest, Robert E.	Minneapolis
	Priestley, James T.	Rochester
†	Prim, Joseph A.	Minneapolis
	Prlina, Isaac M.	Virginia
	Proeschel, Ray K.	Willmar
	Proffitt, William E.	Minneapolis
	Proshek, Lumir C.	Minneapolis
	Proud, Harry S.	St. Paul
	Pugh, David G.	Rochester
	Pulec, Jack Lee	Rochester
	Pumala, Erven E.	Warren
	Purnell, Don C.	Rochester
	Purves, G. Harland	Buffalo
	Puumala, Barbara M.	Cloquet
	Puumala, Reino H.	Cloquet
	Puumala, Ricard R.	Cloquet

Q

†	Quattlebaum, Frank W.	St. Paul
	Quello, Robert O. B.	Minneapolis
	Quiggle, Arthur B.	Minneapolis
	Quimby, Charles W., Jr.	Winona
†	Quinones, Cesar A.	Rochester
	Quist, Henry W., Jr.	Minneapolis

R

	Raab, David E.	Minneapolis
	Raaen, Olaf J.	St. Paul
	Rabcevich, Anatole	St. Paul
	Racer, Harley J.	Minneapolis
	Radke, Robert L.	Montevideo
	Raetz, Sylvester J.	Maple Lake
	Raich, John J.	Minneapolis
	Raile, Richard B.	Minneapolis
†	Rajala, Arnold I.	Youngstown, Ohio
	Ralph, James R.	St. Paul
	Ralston, Donald E.	Rochester
	Ramlow, Ralph M.	St. Paul
†	Ramsey, Walter R.	St. Paul
	Randall, David A.	Minneapolis
†	Randall, Lawrence M.	Rochester
	Randall, Raymond V.	Rochester
	Ransom, H. Robert	Osseo
	Rasmussen, Ramby C.	St. Paul
	Ratelle, Alexander E.	Minneapolis
	Raths, Otto N., Jr.	St. Paul
	Ravits, Harold G.	St. Paul
†	Rawls, William E.	Houston, Texas
	Rayner, Ralph R.	Red Wing
	Rea, Charles E.	St. Paul
	Reardon, Andrew E.	Duluth
	Recht, Thomas M.	Minneapolis
†	Redfield, Nicholas P.	Rochester
	Redleaf, Paul D.	St. Paul
	Reeber, Erick	Bagley
	Reed, Henry H.	Duluth
†	Reed, John H., Jr.	Minneapolis
	Reed, Paul	Virginia
†	Reed, Ralph R.	Rochester
	Reed, Sheldon C.	Minneapolis
	Reese, David F.	Rochester
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	Reff, Alan R.	Crookston
	Regan, John J.	Minneapolis
	Regnier, Edward A.	Minneapolis
	Reichel, Samuel M.	Minneapolis
	Reichelderfer, Charles F.	Staples
	Reichelt, Leland G.	Wadena
	Reid, James W.	South St. Paul
	Reif, Harold A.	Minneapolis
	Reif, Henry J.	St. Cloud
	Reif, Robert W.	White Bear Lake
	Reiher, Jean	Rochester
	Reiley, Richard E.	Minneapolis
	Reinhardt, James H.	Alexandria
	Reiser, Milton P.	Minneapolis
	Reitemeier, Richard J.	Rochester
	ReMine, William H., Jr.	Rochester
	Remole, William D.	Minneapolis
*	Remsberg, Robert R.	Tracy
†	Replogle, William H.	Los Angeles, California
	Resch, Joseph A.	Minneapolis
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	Reynolds, Donald P.	Chicago, Ill.
†	Rheault, J. Gerald	Rochester
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	Rholl, Arnold O.	Minneapolis
	Rice, Carl O.	Minneapolis
	Rice, Fred A.	Minneapolis
	Rice, Hagbart G.	Moorhead
	Rice, William H.	St. Cloud
	Richards, Albert M.	St. Paul
	Richards, William B.	St. Cloud
	Richardson, Edward J., Jr.	St. Paul
	Richardson, Robert J.	Minneapolis
†	Richdorf, Lawrence F.	Minneapolis
	Richter, David J.	Virginia
	Richter, Paul H.	Fergus Falls
	Rick, Paul F. W.	St. Paul
	Rieke, Wellington W.	Wayzata
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	Riggs, Byron L., Jr.	Rochester
†	Riley, Fenwick C.	Rochester
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	Ringhofer, Lawrence	New Ulm
	Ringle, Otto F.	Walker
	Rinkey, Eugene	St. Paul
	Riordan, Elsie M.	Minneapolis
	Ripple, Rudolph J.	St. Paul
	Ripple, Rudolph J., Jr.	Minneapolis
	Risch, Ronald E.	Minneapolis
	Risser, Alden F.	Stewartville
	Ritchie, Donald A.	St. Cloud
	Ritchie, Wallace P.	St. Paul
	Ritt, Albert E.	St. Paul
	Rizer, Dean K.	Minneapolis
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	Roach, Donald E.	St. Paul
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	Roberts, George A.	Austin
	Roberts, Lewis J.	Minneapolis
	Roberts, Oliver W.	Owatonna
	Roberts, Stanley W.	Minneapolis
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†	Robertson, Paul A.	Austin
	Robinson, Cortland O.	Minneapolis
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	Rock, William H.	Anoka
	Rocknem, Robert E.	Minneapolis
	Rockwell, Curtiss V.	Minneapolis
	Rockwood, Philo H.	Fergus Falls
	Rodgers, Richard S.	Minneapolis
	Roehlke, Arthur B.	Elk River
	Roemer, Henry J.	Winona
	Rogers, Charles W.	Winona
	Rogin, Norton	Minneapolis

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	Roholt, Hartvig B.	Bemidji
†	Rohrer, Christian A.	Madison Lake
	Rohrer, Thomas P.	Waseca
	Rolig, David H.	St. Paul
	Rollie, Orris O.	St. Paul
	Rollins, Pat	Minnetonka
	Rome, Howard P.	Rochester
	Romness, Kenneth B.	Mound
	Rondeau, Eugene T.	Two Harbors
	Rooke, Edward D.	Rochester
	Root, Harlan D.	San Antonio, Texas
	Rorem, Joseph A.	Appleton
	Rosenbaum, David L.	Minneapolis
	Rosendahl, Frederick G.	Minneapolis
	Rosenfield, Abraham B.	Minneapolis
†	Rosenow, Edward C., III	Rochester
	Rosenow, John H.	Minneapolis
	Rosenquist, Rudolph J.	Silver Bay
	Rosenthal, F. Harold	Austin
	Rosenthal, Robert	St. Paul
†	Rosenwald, Reuben M.	Minneapolis
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	Ross, James V., Jr.	Rochester
	Rossberg, Raymond A.	Morris
	Rossen, Ralph X.	Minneapolis
	Rossing, Robert G.	San Antonio, Texas
	Rotenberg, Robert J.	Minneapolis
	Rotenberg, Samuel	Huntington Park, Calif.
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	Rovelstad, Randolph A.	Rochester
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	Rowles, Everett K.	Coleraine
	Roy, Phil C.	St. Paul
†	Royals, Daggett O.	Rochester
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†	Rud, Norman E.	Bloomington
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	Rudie, William D.	Duluth
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†	Ruhberg, George N.	Santa Barbara, California
	Ruhe, Albert H.	Willmar
	Rukavina, John G.	St. Paul
	Rumpf, Carl W.	Faribault
	Runquist, John M.	Duluth
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	Russ, Homer H., Jr.	Warroad
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	Ryan, Edward A.	Duluth
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	Ryan, Joseph M.	St. Paul
	Ryan, Patty J.	Minneapolis
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	Rydburg, Wayne C.	Minneapolis
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	Rydland, Arne D.	Minneapolis
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	Rynda, Edwin R.	New Prague
	Rynearson, Edward H.	Rochester
	Rysgaard, George N.	Northfield

S

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	St. Cyr, Kenneth J.	Robbinsdale
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	Salovich, Elmer R.	Minneapolis
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	Sanderson, David R.	Rochester
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	Sanford, Raymond A.	Mankato
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	Sather, George A.	Fosston
	Sather, Richard N.	Fosston
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	Sax, Simon G.	Duluth
	Saxman, Gertrude E. O.	Ulen
	Sayre, George P.	Rochester

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	Scanlan, Robert L.	Rochester
	Scanlon, Hugh A.	Little Falls
	Scanlon, Paul W.	Rochester
	Schaar, Frances E.	Minneapolis
	Schaefer, Joseph F.	Owatonna
	Schaefer, Wesley G.	Minneapolis
	Schaffhausen, Irwin F.	Minneapolis
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	Scherer, L. Raymond	Minneapolis
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	Schiele, Burtrum C.	Minneapolis
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	Schirger, Alexander	Rochester
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†	Schmidt, Hilmar R.	Rushford
	Schmidt, Paul G.	Granite Falls
	Schmidt, Ruben F.	Alden
	Schmidt, W. Robert	Minneapolis
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	Schmitz, Everett J.	St. Cloud
	Schnabel, Robert F.	Crookston
	Schneck, Jack I.	Minneapolis
	Schneider, Lawrence E.	Duluth
	Schnell, Frederick S.	Litchfield
†	Schnell, Roger G.	Rochester
†	Schoch, Robert B. J.	St. Paul
	Schochet, H. Laurence	St. Paul
	Schoeneberger, P. B.	Perham
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	Schoenwetter, William F.	Minneapolis
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	Schultz, Donald O.	Minneapolis
	Schultz, Earl A.	Minneapolis
	Schultz, J. Harold	Minneapolis
	Schultz, Peter J.	Minneapolis
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	Schwartz, Robert K.	Chaska
†	Schwartz, Virgil J.	Minneapolis
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	Schwyzer, Marguerite	St. Paul
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	Scott, Horace	Minneapolis
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	Searl, Richard H.	Faribault
	Seay, James E., III	Minneapolis
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	Seery, Thomas M.	Austin
	Segal, Edward L.	Minneapolis
	Segal, Martin A.	Minneapolis
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	Seibel, David I	Minneapolis
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	Seifert, Gregory L.	Excelsior
	Seifert, Milton H.	Excelsior
	Seifert, Milton H., Jr.	Excelsior
	Seisler, Edward P.	Worthington
	Sekhon, Mohan S.	St. Paul
	Seldon, Thomas H.	Rochester
	Sells, Richard J.	St. Paul
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	Semba, Thomas	Minneapolis
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	Setzer, Hobert J., Jr.	Mankato
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	Shapiro, Stanley W.	Minneapolis
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	Sheppard, Charles G.	St. Peter
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	Sherman, Royal V.	Red Wing
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	Silver, John D.	Minneapolis
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	Skinner, Abbott	St. Paul
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	Spain, W. Thomas	Evansville, Ind.
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	Spang, James S.	Duluth
	Spang, William M.	Duluth
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	Sponsel, Kenath H.	Minneapolis
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	Spraitz, Anton F., Jr.	St. Paul
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	Stahler, Paul A.	Jordan
	Stahn, Louis H.	Fergus Falls
	Stahr, Aubrey C.	Hopkins
	Stam, John	Worthington

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	Steidl, Richard M.	Minneapolis
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	Stein, William A.	Duluth
	Steinberg, Charles L.	St. Paul
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	Steiner, Leon E.	Albert Lea
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	Stenzel, Joseph A.	Minneapolis
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	Sterner, Ernest R.	St. Paul
	Sterner, John J.	St. Paul
	Sterrie, Norman A.	Minneapolis
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	Stewart, Donald E.	Crookston
	Stewart, James R.	Rochester
	Stewart, Marvin J.	Minneapolis
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	Stiegler, Farrell S.	Minneapolis
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	Stiles, Clifford D.	Foley
	Stillwell, George K.	Rochester
	Stillwell, Walter C.	Mankato
	Stilwell, George G.	Rochester
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	Stolpestad, Armer H.	St. Paul
	Stoltz, Robert C.	Minneapolis
	Stone, Norman F.	Minneapolis
	Stone, Stanley P.	Minneapolis
	Storsteen, Kenneth A.	Duluth
	Story, Jim L.	Minneapolis
	Stoy, Robert A.	Little Falls
	Strait, Herbert S.	Minneapolis
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	Stransky, Theodore W.	Owatonna
	Strathern, Carleton S.	St. Peter
	Stratte, Harold C.	Windom
	Stratte, Jon R.	Stillwater
	Strauchler, John	Belview
	Straus, Maurice L.	St. Paul
	Street, Bernard	Northfield
	Streitz, John M.	Duluth
	Strem, Edward L.	St. Paul
	Streu, Richard E.	Minneapolis
	Strewler, Gordon J.	Duluth
	Strickland, Martha J. B.	St. Paul
	Strickler, Jacob H.	Minneapolis
	Strobel, Claire J. A.	Marshall
	Strobel, Jack L.	Minneapolis
	Stroebel, Charles F., Jr.	Rochester
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	Strom, Robert L.	Minneapolis
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	Stromme, William B.	Minneapolis
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	Struck, Clarence A.	Minneapolis
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	Sturges, Robert L.	Minneapolis
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†	Suiter, Ronald D.	Rochester
	Sukov, Marvin	Minneapolis
	Sullivan, C. Roger	Rochester
	Sullivan, W. Albert, Jr.	St. Paul
	Summar, M. Thomas	Virginia
	Summerskill, William H. J.	Rochester
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	Swallen, Thomas O.	Minneapolis
	Swanson, David A.	Minneapolis
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	Swanson, Lawrence J.	West St. Paul
	Swanson, Ralph H.	West St. Paul
	Swedberg, William A.	Duluth
	Swedenburg, Paul A.	Glenwood
	Swedlund, Harry A.	Rochester
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	Sweetser, Theodore H.	Minneapolis
	Sweetser, Theodore H., Jr.	Minneapolis
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	Swendseen, Carl J.	Minneapolis
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	Swensen, Don P.	Duluth
	Swenson, Arnold O.	Duluth
	Swenson, Donald B.	St. Paul
	Swenson, Donald B.	Mankato
	Swenson, Floyd J.	Minneapolis
	Swenson, Orvie J.	Waseca
	Swenson, Richard W.	Minneapolis
	Swenson, Roy G.	North Branch
	Swift, Dean C.	Minneapolis
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	Symmonds, Richard E.	Rochester
	Syverson, Leslie A.	Fergus Falls

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	Tangen, George V.	Minneapolis
	Tani, George T.	St. Paul

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	Tanquist, Edwin J., Jr.	Alexandria
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	Tauxe, Welby N.	Rochester
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	Terry, Howard R., Jr.	Santa Cruz, Calif.
	Tesch, Gordon H.	Elk River
	Teska, Byron A.	Minneapolis
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	Tetlie, James P.	Duluth
	Textor, Jerome	Anoka
	Teynor, Joseph W.	Minneapolis
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	Thelemann, Arthur R., Jr.	Minneapolis
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	Thomas, John V.	Duluth
	Thomas, Juergen E.	Rochester
	Thomas, Russell L.	Rochester
	Thomas, William H.	Long Lake
	Thomes, A. Boyd	Minneapolis
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	Thompson, Arthur	Minneapolis
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	Thompson, Gershom J., Sr.	Rochester
†	Thompson, Gershom J., Jr.	Rochester
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	Thompson, Wayne W.	St. Paul
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†	Thorson, Stephen C.	Vancouver, Canada
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	Thurn, Roy J.	Duluth
	Thysell, Desmond M.	Minneapolis
	Thysell, Harold R.	Crookston
	Thysell, Vernon D.	Moorhead
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	Tobin, John D.	Minneapolis
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	Truesdale, Clark W.	Glencoe
	Tsai, Shih Hao	Minneapolis
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	Turkbas, Nejat	St. Paul
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	Tveten, Omar A.	St. Paul
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	Tyce, Francis A.	Rochester

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	Undem, Dale	St. Cloud
	Underdahl, Laurentius O.	Rochester
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	Utz, Philip H.	Le Crescent

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	Vroman, Donald C.	Minneapolis

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	Walker, Stuart B.	Aurora
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	Walter, William E.	Wanamingo
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	Wangensteen, Owen H.	Minneapolis
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	Watson, Cecil J.	Minneapolis
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	Watson, Robert N.	Detroit Lakes
	Watson, Sidney W.	Little Falls
	Watson, Virgil A.	Detroit Lakes
	Watson, William H. A.	St. Paul
	Watson, William J.	Newport
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	Weber, Lowell W.	Minneapolis
	Wedes, Deno J.	St. Paul
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	Wegleitner, Mark J.	West St. Paul
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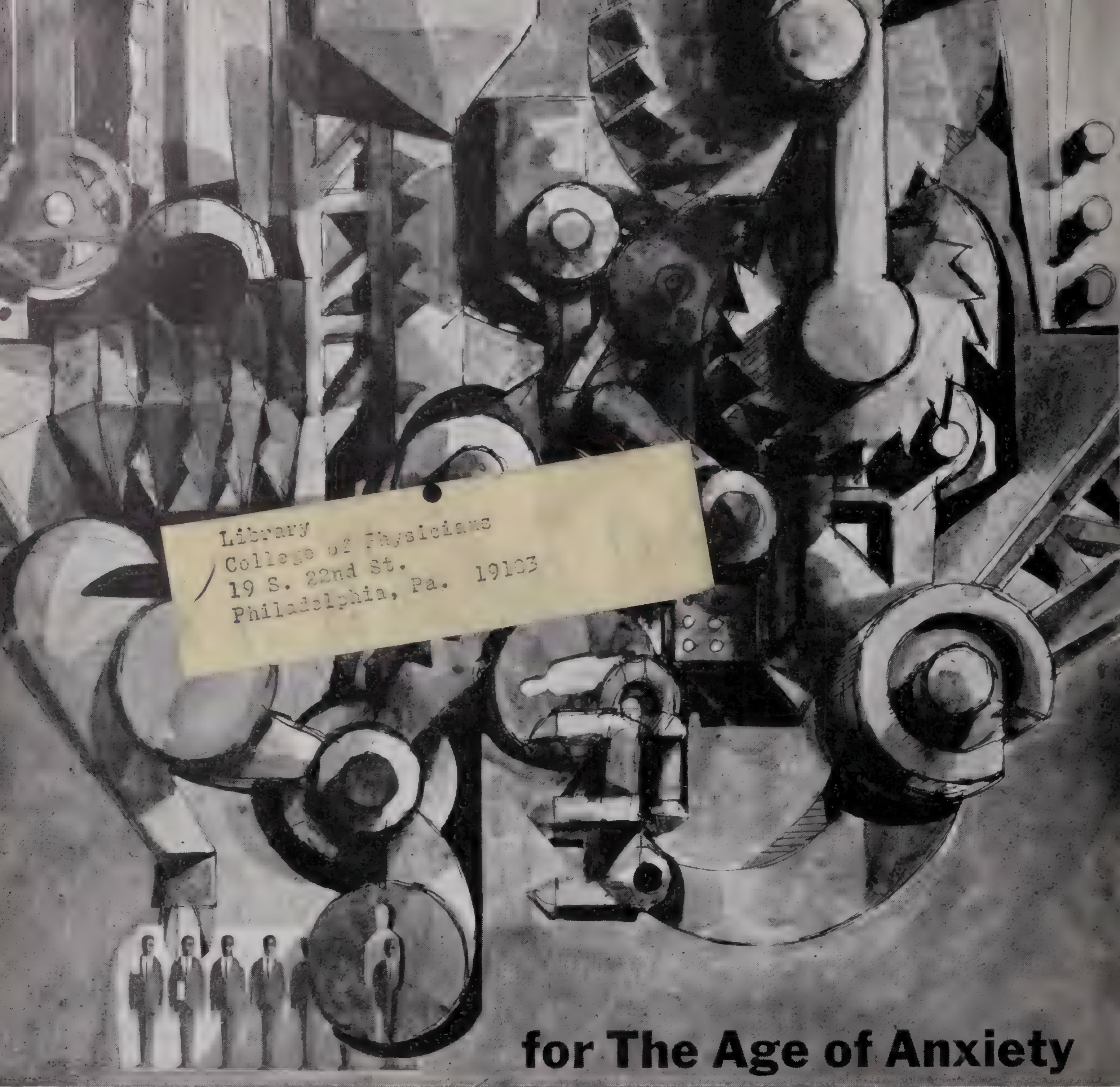
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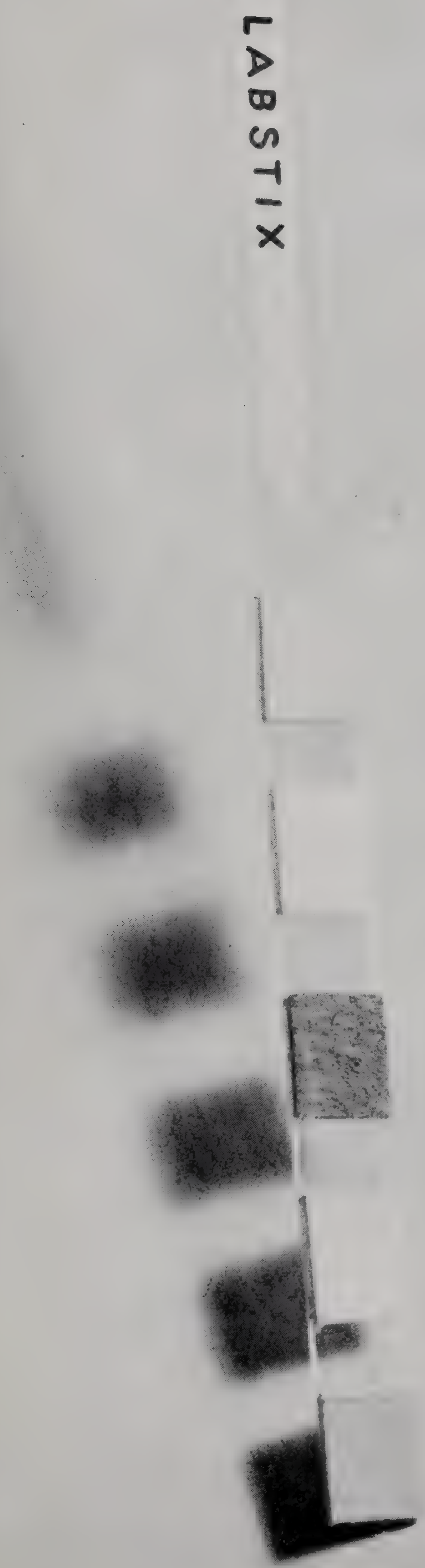

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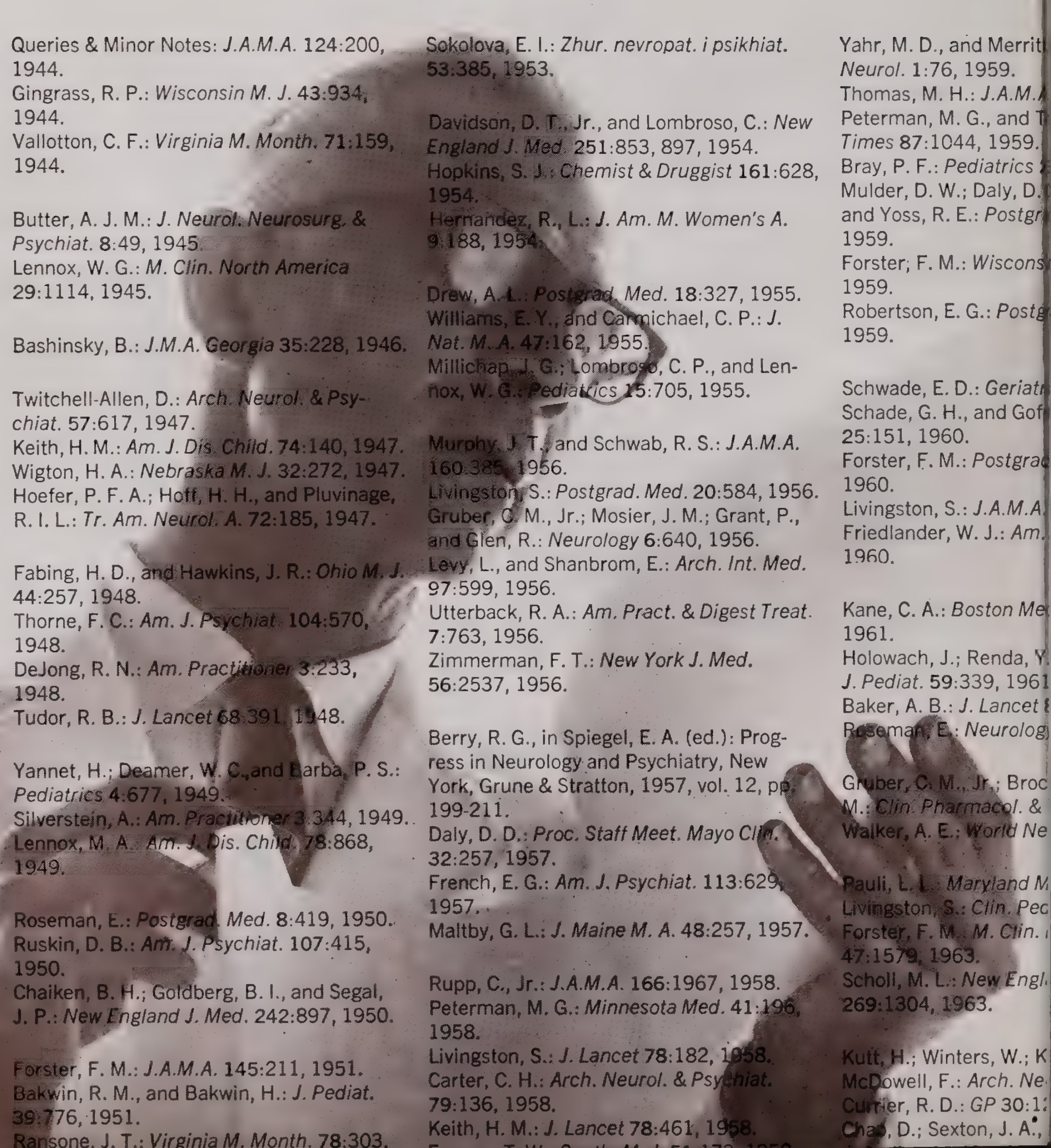

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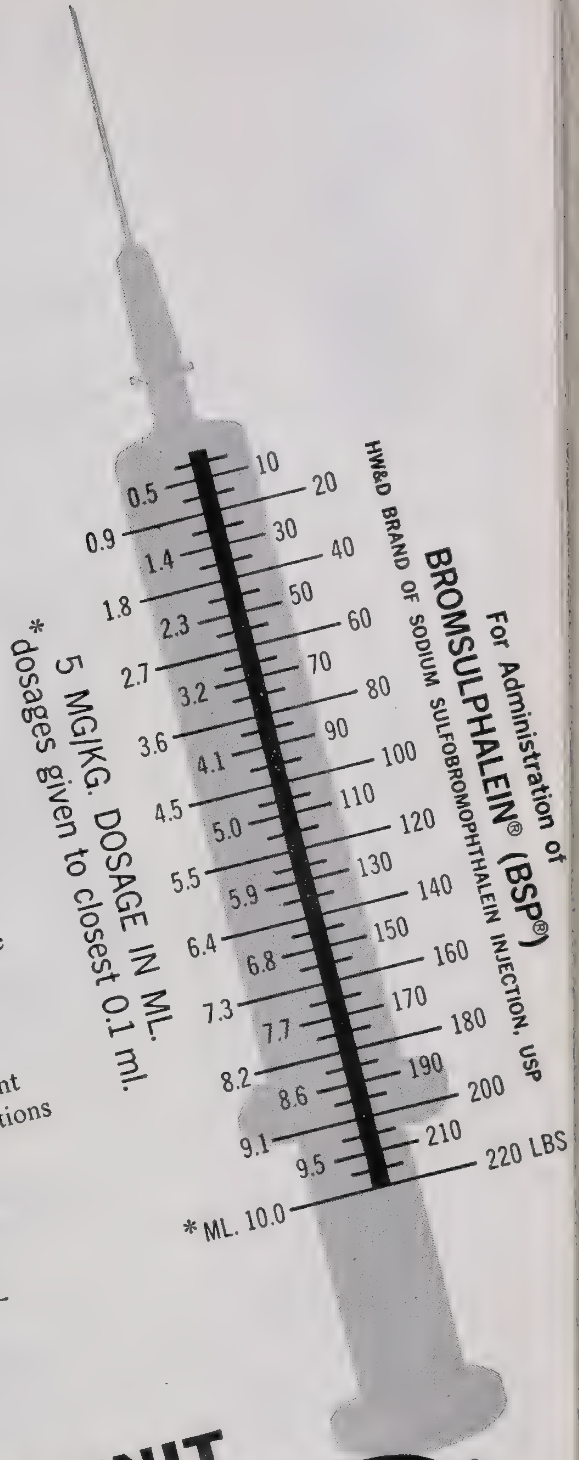

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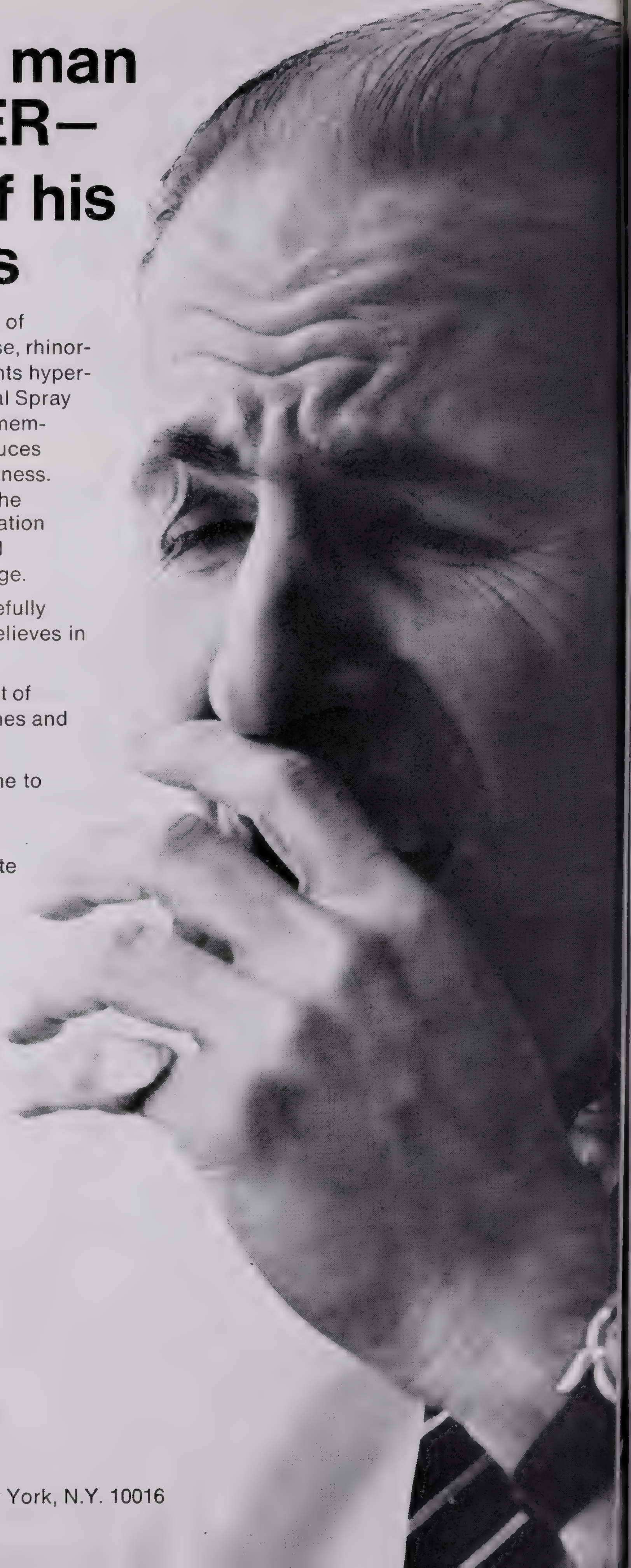

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is often the seat of
low back pain

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and trunk, balanced precariously on a
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dorsal musculature, particularly at th
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and subsequent cross reaction to meprobamate
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President's Letter

Disraeli once remarked that the thing he most wanted to see in any House of Commons member was that he be there. While the Minnesota State Medical Association has always had an excellent attendance at the Annual Meeting, which is continuing contrary to the experience of many state associations, some erosion has been occurring. This is a matter of concern to and constant scrutiny by both the Committee on Scientific Assembly and the Committee on Permanent Evaluation. The basic function of the Committee on Scientific Assembly is the development of a balanced program, the selection and acceptance of qualified speakers, and the arrangement of Round Tables, frequently utilizing speakers featured at the Clinical Sessions. The Committee on Permanent Evaluation, on the other hand, examines the Annual Meeting in all aspects: duration, time of the week and of the month, the banquet and other details, as only one of the many activities of the Association which it considers.

Some of the attrition obvious in all State Association Meetings is the rapid proliferation of specialty group meetings, post graduate courses, and increased hospital and clinic group programs, all intent on providing continuing physician education and equally intent on their own scheduling. The participation of drug firms in the programing, the honorarium for speakers, and the physical arrangements for many of these sessions have brought a new element and a professional touch into previously physician-arranged meetings. As yet no concern over a third party has arisen in this area of medicine in spite of the obvious comparison with other subsidies.

As medicine is reluctantly forced into a new era of patient-physician economics based on services indemnified, not as in the past, by patient-provided hospital-medical-surgical coverage on either a service or an indemnity basis, but rather by governmental decree, medical meetings may assume an entirely new format. Consideration may be given to a separation of the House of Delegates sessions from the clinical program, except in those larger organizations where delegate attendance is a far smaller proportion of the total. The time now necessarily devoted to the constantly expanding rules and regulations under which physicians of the future will practice requires from delegates and officers of all associations an increasing proportion of the actual meeting time, with a consequent decrease in attendance at the Clinical Sessions.

Since no decrease in the socioeconomic demands on physicians is forseeable in the future, some change is inevitable. What changes will occur are not predictable, but both continuing education and continuing physician awareness of these demands are essential. If, in consequence, separation of these two areas of physician participation to avoid overlap is necessary, future sessions could be arranged at different times to give equal emphasis to equally significant demands.

Total physician participation in meetings is never possible, for someone must tend the store; but maximum attendance is a goal.

Continued to page 1142.

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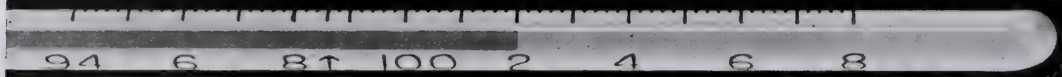

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Echovirus Type 18 Infection

An Unusual Exanthem

PHILLIPS P. WEDEMEYER, M.D.*
MARION K. COONEY, Ph.D.**
JOSEPH W. ST. GEME, JR., M.D.†
Minneapolis, Minnesota

In recent years it has been reported that many of the newly discovered enteroviruses, the Echovirus and Coxsackie virus, may be associated with an exanthem. The usual appearance of these exanthems has been macular or maculopapular, but they may be vesicular, papular, urticarial, or even petechial. Our present knowledge of the clinical features of these viral exanthems has been well summarized by Lerner, Klein, Cherry, and Finland.[1]

In 1959 Medearis and Kramer[2] described a child with a generalized maculopapular rash and Echovirus type 18 viremia. The present report details another instance of exanthem associated with Echovirus type 18 infection. Our patient differs from the original case in that the rash was more prolonged and simulated both erythema multiforme and erythema infectiosum.‡

Case Report

This one-year-old white girl was seen in our clinic on July 9, 1962, because of a rash of two weeks' duration and ataxia of one day's duration.

Two weeks previously she developed a fever of 102° F, and a fine discrete rash appeared on her face and the back of her neck. Mild rhinorrhea occurred after the onset of rash, but conjunctivitis, enanthem, and spread of the exanthem were not discerned by her parents.

Three days prior to her visit fever (102°F) recurred and the rash disseminated with marked involvement of the forehead, nose and back. The child developed anorexia and her stools became scant, thin, watery and foul smelling. Her postauricular lymph nodes were noted to be swollen.

On the day of the initial clinic visit the rash had faded from the forehead and face but had spread

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‡See Test Your Word Score Page 1107.

to the distal arms and legs. The fever and adenopathy were said to have diminished. However, the parents observed that the child was irritable, lethargic, and tended to fall when walking.

Past History

The child had experienced no previous exanthems, cutaneous diseases, or allergic illness. There had been no exposure to drugs or to intense sunlight; nor had there been any recent change in soaps or diet.

Family History

There was no parental history of allergy or recent illness. The household consisted of the patient and her parents, and no known extrafamilial exposure to illness had occurred.

Physical Examination

The child was alert but apprehensive and irritable. Her rectal temperature was 100°F. There was no conjunctivitis or coryza. The pharynx was slightly inflamed. Slight enlargement of the postauricular, cervical, axillary, and inguinal lymph nodes was noted. The liver edge was palpable 3 cm. below the right costal margin and the spleen tip 1 cm. below the left costal margin. Meningismus and other neurologic abnormalities were not detected. Station and gait appeared to be normal.

A discrete, red, maculopapular eruption was observed on the forearms, distal upper arms, and the anterior surface of the trunk and legs. On the right leg hive-like lesions described a circular appearance, closely resembling the iris lesions of erythema multiforme.

The hemoglobin was 11.5 gm.% and the leukocyte count was 8,500/mm^3 with 35% neutrophiles, 56% lymphocytes, 6% monocytes, 1 eosinophile, 1 basophile and 1 plasma cell. A nasopharyngeal culture revealed many pneumococci, and a pharyngeal culture yielded no pathogens. A heterophile antibody determination and toxoplasma dye test were negative.

Clinical Course

The child was seen the next day and the rash was unchanged. She was treated with cool baths only. When seen one week later her rash was fading. At this time it was learned that a male cousin had developed a similar exanthem. Unfortunately, the cousin was not available for study.

Following this visit the family moved and the patient was lost to follow-up until contact was re-established one year later. The patient was healthy and developing normally. The exanthem had not recurred during the elapsed year.

Virologic Studies

The virologic studies were performed according to standard enterovirus methods.[3] A fecal specimen obtained on the 15th day of illness yielded a cytopathic virus in tube cultures of rhesus monkey renal cells. Neutralization tests employing type specific hyperimmune serum identified the virus as Echovirus type 18.

Neutralizing antibody assay was performed with paired acute (15th day of illness) and late convalescent (12 months) sera, using the patient's fecal isolate as the challenge virus. These studies revealed antibody titers of 1:4 and 1:16 respectively.

Discussion

The recovery of the Echovirus type 18 from the stool indicates only that enteric infection or infestation was present. However, this was the only Echovirus type 18 isolation made in Minnesota during 1962. Therefore, the pathogenetic implication of this virus isolation seems more plausible. The fourfold antibody rise supports the acute nature of the infection.

Regarding a differential diagnosis of this child's illness, the following clinical points should be considered. The duration of the rash was too long for any of the usual childhood exanthems except erythema infectiosum.[4] As with erythema infectiosum, the rash began on the face and later spread to the extremities. Although the morphologic nature of the exanthem simulated erythema infectiosum the usual lacelike component was absent, as was plasma eosinophilia.

The illness described by Medearis and Kramer[2] resembled that of our patient in many respects. The exanthem which appeared while the patients were febrile was erythematous, maculopapular, and blanched under pressure. The rash was blotchy, tended to be more discrete than coalescent, and faded without desquamation. There was no enanthem, conjunctivitis, or petechial eruption. Minimal adenopathy was detected. Both cases had loose stools but neither developed serious diarrhea.

The distribution of the rash in our patient tended to be peripheral, whereas for the child reported by Medearis and Kramer the distribution was generalized. The duration of the exanthem in our case was much longer and compatible not only with erythema infectiosum but also with erythema multiforme.

The child described herein re-emphasizes the great variety of exanthemata which may occur with enterovirus infection. Full appreciation of the complete spectrum of illness subsequent to infection with newly recognized viruses must depend in great part upon careful clinical observation and virologic study of abundant patient material. Most of these cases are seen by the practicing clinician who, with the collaboration of community laboratory facilities, has an unexcelled opportunity for productive clinical research.

Summary

The second case report of an exanthem associated with Echovirus type 18 infection is presented. The prolonged, benign exanthematous illness resembled erythema infectiosum, clinically, and erythema multiforme, morphologically.

Acknowledgment

We wish to thank Dr. D. N. Medearis, Jr., of the Department of Pediatrics, The University of Pittsburgh Medical School for kindly reviewing the manuscript.

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WHAT'S YOUR DIAGNOSIS?

This 71-year-old white male walked into the emergency room of the Hospital about 10 P.M. one Friday night because of a 102 degree fever and a "smothering" feeling. He had been seen at home two weeks earlier with a flu-type syndrome but had gradually felt better until the morning of admission. Two years earlier he had had a 90% gastrectomy to control a massive (33 units of blood) bleeding from a gastritis. He had had emphysema for years and had nearly died several times postoperatively: once from a respiratory acidosis and once from a myocardial infarction and heart failure. He had been maintained on digitalis following the surgery but had had no other problems except failure to gain weight.

Physical examination was completely negative. Chest x-ray was normal except for the emphysema. WBC was 13,600 with 80% PMNs. Sputum, and throat cultures grew out normal flora. He was given a broad-spectrum antibiotic on an empiric basis. He felt more comfortable with an oxygen mask but still had a feeling of impending doom. Sixteen hours after admission he was incontinent of urine and stool; a Foley catheter was placed and from that point on until his death 70 hours after admission he passed less than 200 cc. of urine.

Twenty-four hours after admission a few soft rales were heard in each base; his digitalis was increased to 0.15 mgm. daily, and he was given 2 cc. of Salyrgan. This relieved his "smothering" feeling and he needed no more oxygen. Two EKGs were unchanged from the previous admission, and the ancillary lab tests also showed no sign of a recent infarction. Electrolytes obtained after the onset of oliguria were a CO_2 combining power of 26, chloride of 89, and potassium of 6.4 mEq/L.

Forty-eight hours after admission his previously normal blood pressure dropped to zero and he became comatose; his temperature dropped to normal and WBC to 7,400. He was treated with 100 mgm. of Solucortef every four hours and 1 cc. of Aramine every hour, but we could not maintain a systolic pressure of over 90. Levophed by IV drip did maintain an adequate pressure, and dibenzaline 10 mgm. b.i.d. was also given in hopes this would aid the urinary output; but he died 15 hours later without regaining consciousness.

What is your diagnosis? Turn to page 1071.

Humaniculture

In 1906 appeared a book titled Humaniculture by one Hubert Higgins, a man well qualified to write a treatise on health because of the professional posts he held as Demonstrator of Anatomy at the University of Cambridge and Assistant Surgeon to Addenbrooke Hospital, Cambridge, England. The book is unique mainly for its endorsement of Fletcherism, then regarded as a new coefficient in the health equation.

The author maintained that though Fletcherism was an 'ism', it had scientific sanction, as he proceeded to demonstrate by his use of the words poltophagy* and psomophagy,* two contrasting methods of ingesting food. He pointed out that the chewing and swallowing mechanisms of the herbivorous horse and the carnivorous dog show a sharp physiological difference, the horse being obliged to masticate and insalivate his food thoroughly before swallowing; but not so the dog, who tears off morsels and swallows them with almost no chewing. Hence the horse is a poltophagist and the dog a psomophagist.

Man, however, is neither poltophagic nor psomophagic exclusively. Structurally and metabolically he falls somewhere between, favoring the horse, however, more than the dog, which means that for optimum nutrition it is incumbent on him to chew his food longer and better than he habitually does.

Furthermore, Higgins contended that thorough mastication reduces the amount of food man needs; and consuming less, he will be healthier, feel more energetic, and function more efficiently.

While Higgins did not advocate counting mastications, he pointed out that Mr. Gladstone attributed his phenomenal strength and endurance to the practice of poltophagy to the tune of thirty to thirty-five chews for each mouthful of food (an estimate later amended, however, by an interested observer who counted sixty to seventy jaw movements on the part of the prime minister).

Nor did Higgins recommend hyper-mastication, which would invest the process of chewing and swallowing with such prolonged and tedious attention as to detract needlessly from the gustatory pleasure of eating.

While Humaniculture (1906) may be gathering dust on library shelves and Fletcherism may be obsolete, poltophagy remains a good word for a practice which might more profitably be engaged in by the all too numerous affluent and corpulent Americans these sixty years later.

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*See Test Your Word Score Page 1107.

On Coral

Thirteenth century Vincent of Beauvais, in his enthusiasm over the therapeutic virtues of coral, claimed that it checked hemorrhage, reduced corpulence, drew harmful humors from the eye, cured ulcers, and benefited heart, intestines, and spleen. Suspended over the mouth it stopped stomach-ache; suspended from the neck it prevented epileptic fits.

— Lynn Thorndike in A History of Magic and Experimental Science

Progress

The fundamental rule of progress is to do what you can with what you have, where you are today. — R & R Magazine

Primary Hyperpara—Thyroidism

The Importance of Early Diagnosis

LAURENCE E. WINTER, M.D.*
DONALD G. MC QUARRIE, M.D.*
Minneapolis, Minnesota

PRIMARY HYPERPARATHYROIDISM is an uncommon, though not a rare disease. Since Mandl[1] removed the first parathyroid adenoma in 1926, hyperfunctioning parathyroid tissue has been sought with diligence by surgeons throughout the world. There are now several series[2-4] of over 100 cases, and general awareness of the disease's clinical features has increased. The correct diagnosis, however, is all too often not entertained until the disease becomes advanced. The early symptoms of primary hyperparathyroidism: polyuria, polydipsia, anorexia, fatigue, weakness, headache, constipation, and mental imbalance are so protean** as to rarely lead to a diagnosis. However, examination of the case presented below would suggest that more careful attention paid to the early symptoms can result in an earlier diagnosis and the avoidance of serious late complications.

It is the purpose of this paper to present the recent experience of this hospital with cases of primary hyperparathyroidism which came to surgery, and to emphasize clinical features of the disease which can facilitate an earlier diagnosis.

Material

The present series is composed of 24 patients between the ages of 23 and 75, with a mean age of 51.5 years. Most large series are composed of approximately three women to one man. But since the population of this hospital is almost exclusively male, no cases were encountered in women.

The study covers the period 1948 to 1964, during which time there were 164,142 admissions. The 24 cases represent an incidence of approximately one in 7,000 admissions.

---

*Department of Surgery, Minneapolis Veterans Administration Hospital and the University of Minnesota, Minneapolis, Minnesota.

**See Test Your Word Score Page 1107.

Clinical Features

Each patient presented with a complex of symptoms involving multiple systems (Table 1). A renal calculus was the most frequent complication and was encountered in all but three patients. Three of the patients with musculoskeletal pain as a chief complaint had x-ray evidence of bone cyst formation. In all, 11 patients showed x-ray indication of decreased lamina dura of the teeth and/or bone cyst formation. The diagnosis of peptic ulceration was arrived at by laparotomy or x-ray demonstration. Six of the seven ulcers occurred in the duodenum and were all particularly refractory to conservative treatment. An incidental finding involved a patient being treated for a recent stroke with a history of renal stones in the past.

Table 2 summarizes the prominent clinical features which accompanied the chief complaints and which predated diagnosis by an average of seven years in this series. In addition to the expected high frequency of urinary and musculoskeletal system involvement, attention is called to the relatively high frequency of the less commonly appreciated symptoms such as anorexia, headache, polyuria, constipation.

TABLE 1
Incidence of Chief Complaints

Symptom	Incidence
Renal stone	11 (48.3)
Musculoskeletal	7 (29.2)
Ulcer	3 (12.5)
Mental illness	2 (8.3)
Incidental	1 (4.2)

TABLE 2
Incidence of Symptoms Accompanying the Chief Complaint

Symptom	Incidence
Renal Stone	21 (87.5)
Constipation	16 (66.7)
Headache	14 (58.3)
Musculoskeletal	13 (54.5)
Anorexia	13 (54.5)
Polyuria and polydipsia	11 (48.3)
Hypertension	9 (35.5)
Fatigue and weakness	8 (33.3)
Mental illness	6 (25.0)

TABLE 3
Incidence of Pathology

Tissue	Incidence
Single adenoma	19 (79.2)
Double adenoma	1 (4.2)
Carcinoma	0 (0.)
Primary hyperplasia	4 (16.7)

Laboratory Diagnosis

A number of rather elaborate tests and measurements have been devised in an attempt to distinguish the hyperfunctioning parathyroid state from other similar conditions.[5-10] At present, there is no clinically available method of assaying parathormone blood levels in man; thus the level of gland activity must be inferred from the effects of the hormone on calcium and phosphate metabolism.

Serum Calcium

The most useful screening test in this series was the serum calcium level. Determinations on patients in this series ranged from 9.2 to 20.2 mgm/100 cc. Each patient, however, had at least one value over 11.1, and 20 of the 24 patients had at least one value over 11.6.

Serum Phosphate

The serum phosphate level was frequently raised by the renal damage commonly observed with hyperparathyroidism, thus masking the classic hypophosphatemia. In nine cases the serum phosphate level was consistently below the lower limits of normal; but in two others it was above the upper limits of normal on at least one determination.

Urine calcium levels reflected the serum levels and were abnormally high on at least one determination in each case. At this institution, serial serum calcium determinations have given the most reliable screening and confirmatory assistance. The alkaline phosphatase was abnormally high in six cases, and 12 patients had elevated blood urea nitrogen. The tubular reabsorption of phosphate test was performed in 12 cases and was low in seven.

Pathology

Table 3 summarizes the histologic changes in the glands. Twenty (83.3%) of the 24 cases were due to adenomas. Of the 21 adenomas recovered, 16 were formed predominantly of chief cells, and five of water-clear cells. The lower pair of glands was involved in 76% of the cases. In only one instance was it necessary to perform mediastinal exploration to recover the adenoma. Primary hyperplasia was encountered in four cases, all of which were made up predominantly of clear cells. There were no cases of parathyroid carcinoma. One case was suggestive of the multiple endocrine adenomata syndrome in that the patient had had a symptomatic islet cell adenoma of the pancreas removed 14 years prior to removal of a chief cell adenoma.

Case Report

A 35-year-old colored waiter was first worked up at this hospital for complaints of nausea, constipation, abdominal pains of a vague nature, and dull leg pains. Physical examination and an upper G.I. series were unremarkable. The patient was discharged with a diagnosis of lumbosacral myofasciitis. He returned two years later with the same above complaints and a persistent frontal headache. This time he was discharged without specific treatment, only to return the following year with the same problems. He was then felt to have an organic neurologic disease, type undetermined, and received antiluetic therapy. A salivary calculus was noted on that admission. The patient returned to work but had gradual progression of musculoskeletal pain which became generalized.

Sixteen years after originally seen, the patient noted the onset of polyuria and polydipsia to such a degree that his work was interfered with. Bone pain, weakness, and fatigue became so severe that he became essentially an invalid.

The patient returned for his fourth admission 21 years after first seen. He was noted to be a thin, feeble, colored man appearing 20 years older than his stated age. Blood pressure was 165/105. There was marked weakness of all muscle groups. A one-cm. mass was palpated in the left lobe of the thyroid gland. Serum calcium was 17.5, serum phosphorus 4.5, alkaline phosphatase 72, BUN 40; and 24-hour urine collections for calcium were 512 and 300 mgm. on a Bauer-Aub diet. An IVP revealed a calcification of the lower pole of the left kidney and nephrocalcinosis. X-rays of the long bones revealed polycystic changes. The patient was taken to surgery where a chief cell adenoma was removed.

Over the next two months, the patient's bone films improved markedly, and his bone and abdominal pains resolved. He became mentally clear and ambulatory for the first time in several years. Two years later, however, he returned with continued complaints of headache, a blood pressure of 190/126, and early congestive failure. He became well enough to leave the hospital, but returned the next year confused, dehydrated, febrile, with a blood pressure of 178/110, a BUN of 125, and a serum phosphorus of 10. He deteriorated rapidly and died on the third hospital day. Post-mortem examination revealed far advanced renal disease.

Discussion

Complaints referable to the urinary and musculoskeletal systems are the most common antecedents to the diagnosis of hyperparathyroidism.[11,12] The striking feature of Table 2, however, is the high incidence of less commonly appreciated symptoms. The appearance of these symptoms usually predated the diagnosis by several years, but their significance was not properly appreciated by either the patient or the physician. It should be emphasized that the nonspecific symptoms, as in the above case, were usually a prominent part of the history, and were on occasion so severe that the patient was incapacitated. It would seem that if earlier diagnosis is to be made, more attention must be given to the less specific symptoms. Any one or two of these symptoms alone are too protean to suggest hyperparathyroidism; however, a combination of these complaints should arouse the suspicion of hyperparathyroidism and warrant a serum calcium determination.

Summary

Twenty-four cases of primary hyperparathyroidism are presented in which the diagnosis was confirmed by surgery. Arrival at an earlier diagnosis through a higher index of suspicion when presented with the early symptoms of the disease is emphasized.

We wish to express our thanks to E. W. Humphrey, M.D. for his help in preparing this paper.

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IT'S THE LAW
Recent Court Decisions Tend to Favor Patients*

A New York housewife was burned by x-ray treatment for bursitis. Years later another doctor warned her that the scars could develop cancer. She sued the radiologist and collected $25,000. Ten thousand was awarded for the burns and $15,000 for the cancerophobia she developed. The New York court of appeals ruled that the wrongdoer is liable for the ultimate result.

Extending malpractice damages to cover mental disturbances is only one of a number of new legal doctrines; some lawyers maintain that the rules have too long favored the doctors. Attorney Lou Ashe, a San Francisco lawyer and partner of the much publicized Melvin Belli, states: "Some judicial inroads are being made on previous inflexible rules of proof" which have protected doctors. Doctors and defense lawyers are coming perilously close to the principle that doctors would be financially liable for unsuccessful treatment whether they are negligent or not.

A New Yorker recently brought a successful suit against a medical laboratory for mental anguish caused by an inaccurate report that he was sterile. The state court of appeals observed: "Freedom from mental disturbance is now a protected interest in this state."

Of more widespread import are new rules breaching heretofore important defense procedures. Previously, a patient had to produce a doctor to prove his claim. A California judge complained that a plaintiff in a malpractice suit could get testimony only from an occasional "lone wolf" willing to risk ostracism by his fellow practitioners and cancellation of his insurance policy. Some courts are now permitting exceptions to the rule requiring medical testimony. One such exception is on the principle of "res ipsa loquitur," meaning "the thing speaks for itself." Judges are ruling that expert medical testimony is not necessary when the patient suffers obvious injuries; the injury speaks for itself and the defendant must accept the burden of defense. A landmark case occurred in San Francisco where a housewife suffered a facial paralysis following a mastoid operation. During the trial no medical evidence was introduced to the effect that the surgeon was negligent. The defense testimony showed that the injury though rare did occur unavoidably in a small percentage of mastoid operations. The judge, on the basis that the injury to the nerve was obvious, put the question to the jury, which awarded $40,000 to the patient. This decision was upheld by the California court of appeals.

It is quite evident that because of the very large awards given against doctors, the old $25 yearly premium for $10,000 to $25,000 policies is outdated.

Stanley R. Maxeiner, Sr., M.D.
Minneapolis, Minnesota

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*Wall Street Journal, July 12, 1965.

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The psychologist has been slanderously defined as a man who tells you what everybody knows in language nobody can understand. — Joseph Jastrow

Sarcoidosis

Complicated by Chylothorax

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MERLE BAH, M.D.**
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NONE OF OUR concepts solves the riddle of sarcoidosis today, as the etiology and pathogenesis still remain obscure. It seems that sarcoidosis with its many strange features belongs to a borderland with similarities to established infections and still etiologically obscure conditions as collagenoses, Hodgkin's disease and real tumor disease."[1]

Case Report

A 79-year-old negro female was admitted for the first time in September, 1960, with a history of nausea, vomiting, weakness and a 16-pound weight loss of several months' duration. Generalized pruritus was present since the late 1950s without evident skin lesions. No history of bleeding, dyspnea, cyanosis or wheezing was obtained. Peripheral edema was questionably present in the mid-1950s. She had been taking digitalis irregularly since then.

Physical Findings

The physical examination revealed an elderly, well-developed, well-nourished negro female in no acute distress. The pertinent positive findings included very dry skin, swelling of the distal interphalangeal joints, grade III/VI systolic murmur with maximum intensity at the base of the heart, and liver palpable 3 cm. below the costal margin at the right midclavicular line. The lungs were clear. No tumor masses, splenomegaly or lymphadenopathy were palpated. No skin lesions were observed. Neurological examination was within normal limits.

Laboratory Studies

The hemoglobin was 8.7 gm.%, red blood cell count was 3.1 million, reticulocyte count 2.8%, and white blood cell count 8600 with a normal differential.

Urinalysis showed specific gravity of 1.010 on several occasions but was otherwise negative.

The erythrocyte sedimentation rate was 92 mm. in one hour. Serum electrophoresis revealed a slight increase of gammaglobulin, but the total serum protein was normal. Serum calcium was 11.5 mg.%, serum phosphorus 7.0 mg.%, alkaline phosphatase 9.6 units (King-Armstrong), blood urea nitrogen 58 mg.% and serum creatinine 4.3 mg.%. Sodium,

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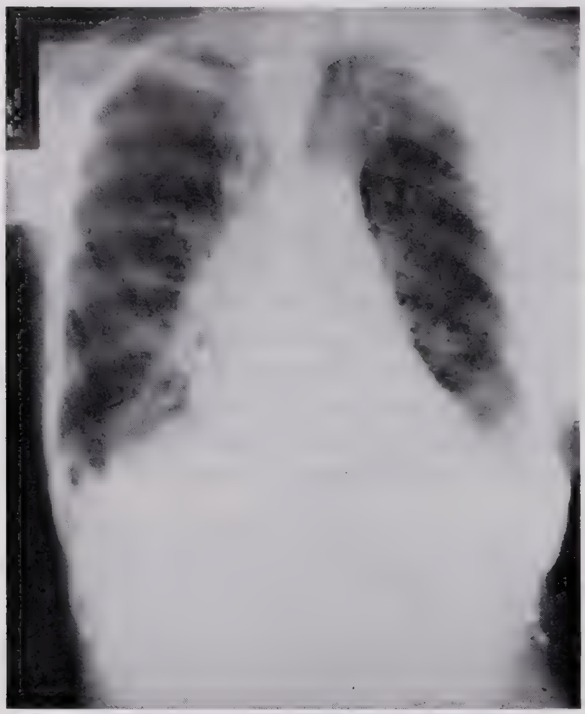

Fig. 1 — Slight emphysema and basilar fibrosis are seen. To the left the partly calcified axillary tumor is just visible. In the left supraclavicular region another calcified mass is observed.

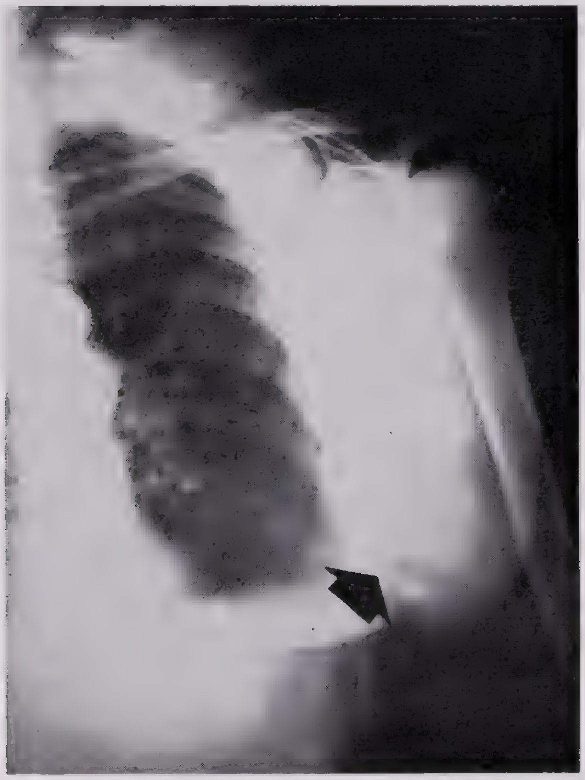

Fig. 2 — The left axillary mass is here seen. Note the layering of calcium in the dependent portions of the tumor.

potassium, chloride and bicarbonate in serum were within normal limits.

The bone marrow aspirate showed an anemic pattern but was otherwise not diagnostic.

Upper gastrointestinal and colon x-rays were essentially negative. Chest x-ray showed mild pulmonary emphysema and basilar fibrosis.

Progress

After the above work-up, the patient received oral iron and blood transfusions and was discharged with the diagnosis of nonspecific anemia. The digitalis was discontinued upon admission.

She was followed in the outpatient department at regular intervals. Her anemia persisted and she complained of progressively increasing pruritus, which a dermatologic consultant was unable to explain.

Second Admission

The patient was again admitted in May, 1961, with history of a tumor mass above her left iliac crest first noticed one month previously. The mass was nontender, firm, smooth, attached to the skin and to the underlying structures, and measuring 5 cm. in diameter. The physical examination also revealed a similar mass of about the same size in the left axilla. Roentgenologic studies showed both the masses to be calcified.

The iliac tumor mass was biopsied and showed a cyst-like formation with foreign bodies like granulomas. The patient refused biopsy of the axillary mass.

Third Admission

The patient was readmitted in August, 1962, because of pain in the left axillary mass. The physical examination now showed a mass of 2 cm. in diameter in the left supraclavicular region, a mass of 2-3 cm. in diameter on the left thigh, in addition to the other lesions, earlier described, which had not changed in size.

The axillary mass was aspirated and 75 cc. of salmon-colored fluid was obtained. Cultures were negative for bacteria, including acid-fast bacilli, as well as for fungi.

Upright films of the left axilla and supraclavicular areas showed loculation of the masses which contained calcium-like densities which layered out in the dependent portions of the masses.

A bone survey x-ray was essentially negative.

A venogram of the left arm showed no venous connection with the tumor.

The hemoglobin was 10.6 gm.%. White blood cell counts were within normal limits. Cell differential counts now showed an elevation of eosinophils to 11, 6 and 5 % on three examinations.

Urinalysis showed + for albumin on several occasions.

Serum calcium was 12.3 mg.%, serum phosphorus 6.9 mg.%, and alkaline phosphatase 4 and 6.9 units (King-Armstrong). Twenty-four hour urinary calcium excretion was repeatedly within normal limits. The erythrocyte sedimentation rate was 50 mm. in one hour. The protein-bound iodine was 6.6 microgm.%. Bromsulphthalein was 1.2% retention at 45 minutes. The electrocardiogram was within normal limits except for an incomplete right bundle branch block.

Final Admission

Except for increasing weakness the patient noted no particular change in her symptoms until spring, 1963, when the tumors in the left axillary and supraclavicular regions appeared to increase rather rapidly in size. The patient was admitted to Bethesda Lutheran Hospital, St. Paul, in July, 1963.

The left supraclavicular mass now measured 10 cm. in greatest diameter and the axillary mass was slightly larger.

Flat and upright x-rays of the supraclavicular and axillary regions showed loculated fluid containing masses with calcium-like densities (Figures 1 and 2).

The left knee showed a soft tissue calcification similar to that in the axilla (Figure 3).

A film of the abdomen revealed normal-sized kidneys with no renal calculi demonstrated.

The described tumor near the left knee was biopsied. The microscopic examination showed "dense fibrous tissue with relatively acellular structure. The inner surface of the cystic lesion was covered by an irregular layer of granular material identified as calcium. There were a few foreign body giant cells present."

No essential change was recorded this time. The blood urea nitrogen, however, had increased to 76 mg.%. The serum calcium was between 11.0 and 12.5 mg.% on several occasions. The twenty-four hour calcium excretion in the urine was constantly within normal limits. The serum protein was 5.6 gm.% with an albumin/globulin ratio of 1/1.07.

Hospital Course

The patient had a few episodes of paroxysmal atrial fibrillation during this hospitalization. She converted to sinus rhythm with digitalis and was maintained at normal sinus rhythm on low maintenance dosage. She had on one occasion a transient elevation of the blood pressure from normal level to systolic greater than 300 mm. Hg, but she was successfully treated with reserpin.

During the hospitalization the patient's condition was characterized by increasing

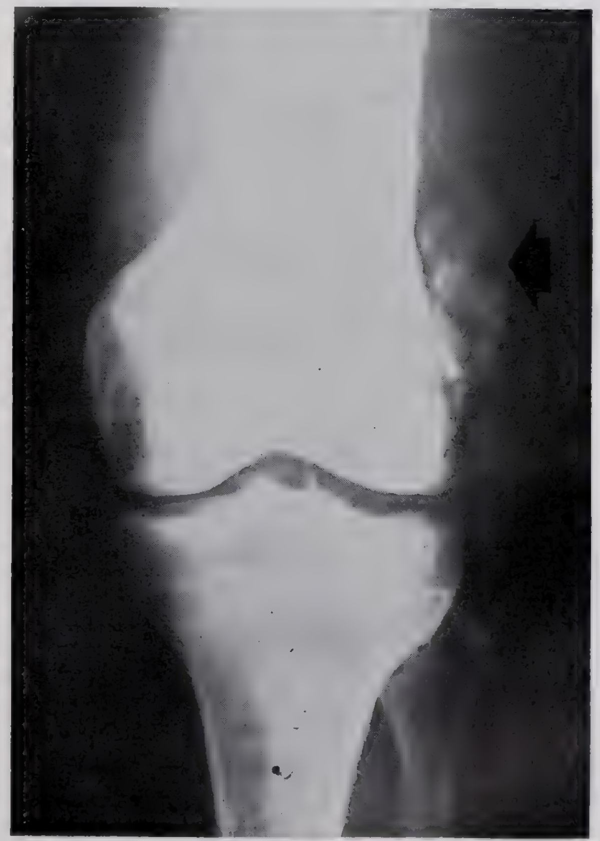

Fig. 3 — Calcification in the soft tissue adjacent to the left knee.

weakness and episodes of unconsciousness and confusion. She gradually deteriorated and suddenly expired.

Necropsy Findings

The post-mortem examination showed that the axillary and supraclavicular masses were multiloculated cystic tumors filled with salmon-colored fluid with a slight granularity. The cyst wall was 6-10 mm. thick and fibrinous in consistency. Numerous mediastinal lymph nodes up to 2 cm. in diameter were found, with a particularly prominent group of nodes at the root of the great vessels. The lymph nodes were on the superior and anterior surfaces of the left subclavicular vein and encompassed the thoracic duct. This region was very densely scarred. In the left thoracic cavity there was approximately 2000 cc. of milky fluid. The liver was slightly enlarged, weighing 1850 gm. The spleen appeared tannish-brown and had an increased fibrous consistency.

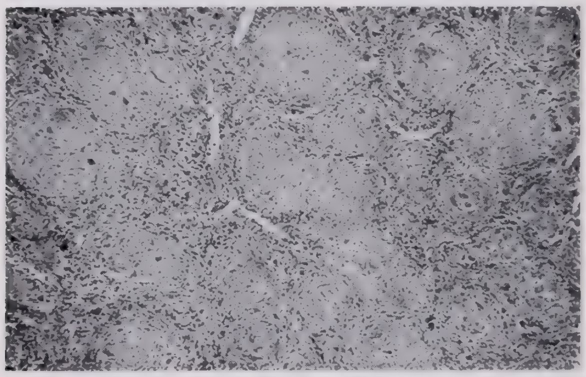

Fig. 4 — Section of spleen. Noncaseous granulomas are scattered all over the picture. (40 x)

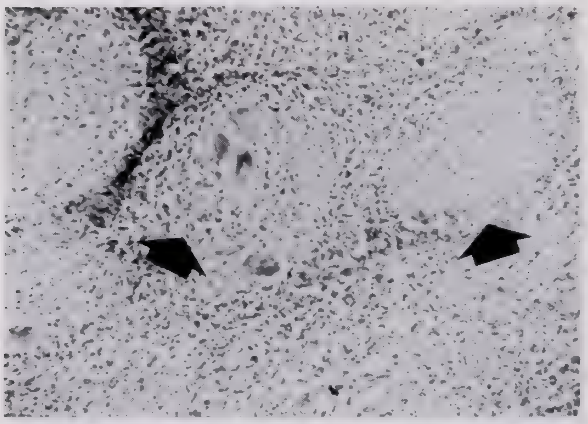

Fig. 5 — Spleen. Higher magnification of granulomas. (100 x)

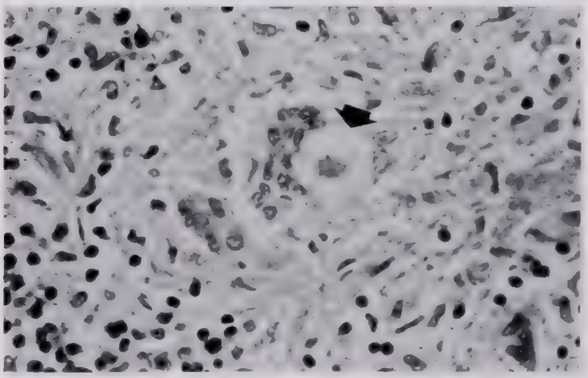

Fig. 6 — Multinucleated giant cell with an "asteroid" inclusion body can be seen in the centre of the picture.

The necropsy conclusions were as follows:

1. Sarcoidosis involving anterior superior mediastinal and thoracic lymph nodes, obstructing the thoracic duct and involving the liver and spleen (Figures 4 and 5). The axillary cyst wall showed giant cells and many areas of calcification (Figure 6).
2. Arterionephrosclerosis and macroscopic tubular calcification.
3. Left chylothorax — secondary to obstruction of the thoracic duct.
4. Old degenerated thyroid adenoma.
5. Pulmonary emphysema.
6. No malignancy was found. The parathyroid glands were identified and normal.

Clinical and Pathological Discussion

The patient had a persistent, marked elevation of her serum calcium. Evaluation of the etiology of this abnormal finding led us to the following differential diagnoses:

1. Primary hyperparathyroidism. 2. Malignant disease with or without metastases to the bones.[2-6] 3. Sarcoidosis. 4. Hyperthyroidism. 5. Paget's disease. 6. Milk-alkali syndrome. 7. Immobilization. 8. Vitamin D intoxication.

Vitamin D intoxication, immobilization, and milk-alkali syndrome can be promptly excluded in view of the lack of history. Laboratory findings and x-ray studies also eliminate Paget's disease.

Hyperparathyroidism

This diagnosis was not excluded pre mortem. X-ray studies and some laboratory results, however, did not support the diagnosis.

Bone survey x-ray did not show any osteoporosis, osteosclerosis, or punched-out areas in the distal phalanges.

The urinary excretion of calcium was always normal and not elevated as might have been expected. A normal excretion of calcium frequently occurs in advanced hyperparathyroidism with impaired renal function.

The serum phosphorus was elevated and not decreased, as is often seen in this disease. An elevated serum phosphorus, however, can be found when the kidney function is impaired and often in elderly patients or in sarcoidosis.[7] The alkaline phosphatase was normal, which is the rule in hyperparathyroidism without bone lesions. It should be emphasized that hypercalcemia may be the only abnormal laboratory finding in hyperparathyroidism.[8,9]

Consequently this disease was not ruled out pre mortem. No steroid administration test was performed.[10] The autopsy findings, however, showed normal parathyroid glands.

Malignancy

The patient's age favored a malignancy. Severe pruritus is occasionally accompanied by a malignant disease. Malignancies of the breast, lung, kidney, ovary, prostate and pancreas as well as malignant lymphoma, multiple myeloma and leukemias with or without bone metastases can produce hypercalcemia.[2-6]

Furthermore, extensive soft tissue calcifications have been reported in cases of carcinoma in the gastrointestinal tract.[11] Finally, the clinical course in this case is also consistent with a malignant disease. The biopsies as well as the autopsy were negative for malignancies.

Hyperthyroidism

Hyperthyroidism rarely causes hypercalcemia. The patient did not manifest any clinical evidence of hyperthyroidism. She repeatedly had episodes of slow atrial fibrillation readily converted to sinus rhythm with digitalis, which would tend to rule out hyperthyroidism as a cause of the atrial fibrillation. Repeated normal values of protein-bound iodine and normal basal metabolic rate also opposed the diagnosis of hyperthyroidism. At autopsy the thyroid gland was normal except for an old degenerated adenoma.

Sarcoidosis

This patient presents with subcutaneous masses, hepatomegaly, hypercalcemia, hypergammaglobulinemia and azotemia. These are not infrequently reported findings in sarcoidosis—at least in this country.[12] Hypercalcemia has been reported in 20-30% of sarcoid patients in the United States and in 10% in a communication from England.[13-15] Sarcoidosis may involve any organ, but most frequently seen clinically are:[12] lung, 40-85%; mediastinal and/or hilar adenopathy, 57-100%; liver, 6.9-43%; spleen, 8.2-42%; peripheral lymph nodes, 37-100%; skin and subcutaneous tissue, 7.1-63%.

The biopsies were very suggestive of sarcoidosis. However, the normal chest x-ray without hilar lymphadenopathy combined with the unusual roentgenological appearance of the tumors produced a confusing picture.[16,17] Large calcifications are very rare in sarcoidosis[18] but are occasionally seen in tuberculosis. Calcifications in sarcoidosis are commonly small and eggshell-shaped in the lung or in a lymph node.

Furthermore, the formation of cavities in the soft tissue was puzzling. Cavities in lungs with sarcoidosis have been reported sporadically but are rare.[19] Some of these reported cavities have also contained fluid more or less hemorrhagic in character. In one case secondary fungal infection was reported in a sarcoidosis patient with a pulmonary cavity.[20,21]

The post-mortem examination revealed a left chylothorax secondary to obstruction of the thoracic duct by enlarged scarred granulomatous lymph nodes.[22] Thoracic duct obstruction has been seen in malignancies and tuberculosis, but to our knowledge it has not been previously described in a case of sarcoidosis. A similar obstructive phenomenon attributed to sarcoidosis has been reported as a cause of portal hypertension with esophageal varices.[23]

Sarcoidosis is now considered to be a

nonspecific entity characterized by the granulomatous appearance of tissues. Many agents have been implicated in the etiology of the reaction, such as bacteria, fungi, foreign bodies, chemicals and different tumors. Its immunological resemblance with Hodgkin's disease is noted.[24] It is likely that more specific etiological factors will be discovered, and accordingly fewer cases will occur in the broad category now called sarcoidosis.[25,26]

Summary

A case of sarcoidosis with some interesting necropsy findings is presented. An elderly negro female was admitted with a history of fatigue, vomiting and generalised pruritus. The positive findings in her work-up were hepatomegaly, hypercalcemia, anemia, azotemia and hypergammaglobulinemia. She also developed during a three-year period subcutaneous, partly calcified tumors, the biopsies of which showed a granulomatous tissue with foreign body giant cells. Pulmonary changes and hilar adenopathy were clinically absent. A downhill course similar to that seen in malignancies occurred.

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ANSWER TO WHAT'S YOUR DIAGNOSIS

(From page 1059)

Classical bilateral severe necrotizing bronchopneumonia. It is possible in early pulmonary disease to have a normal x-ray finding. With continuing symptoms, a repeat of the chest films should be done, because pneumonia can always be identified on the x-ray film. Cultures were not taken, as the autopsy was done at the mortuary and the body had already been embalmed.

He also had a severe nephrosclerosis and severe coronary sclerosis with an old (two-year) myocardial infarction.

Derivatively Speaking

Catarrh — from Greek *katarrhein* (to flow down)

Acute Myeloid Leukemia

Treatment of with 6-Mercaptopurine and Cyclophosphamide*

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THE CURRENT DRUG therapy for acute leukemia utilizes only a few specific chemotherapeutic agents as well as such nonspecific measures as antibiotics, transfusions, and adrenocortical steroids. By far the most successful of the chemotherapeutic agents has been 6-mercaptopurine. Its use since 1952 has significantly prolonged survival, particularly in children with acute lymphocytic leukemia.[1] Unfortunately this improvement in prognosis is much less evident in adults; current figures list the average survival in all types of acute leukemia as under five months.[2] These facts stimulate a continued search for a more effective therapy.

The prolonged use of 6-mercaptopurine in the control of acute myeloid leukemia frequently cannot be attained under circumstances in which the platelet count is below 50,000 cmm. The thrombocyte-depressing effect of 6-mercaptopurine accentuates the already existing thrombocytopenia. Therefore, in the presence of thrombocytopenia, short courses of 6-mercaptopurine were utilized for five to ten days at weekly intervals without the complication of further platelet depression. This attempt failed to produce any significant change in the leukemic process.

It was therefore considered that the use of this short-term course of 6-mercaptopurine might be aided by the concomitant use of some other cytotoxic compound. Since cyclophosphamide appeared to have a platelet sparing effect, single massive doses of intravenous cyclophosphamide were employed in combination with short courses of

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6-mercaptopurine in ten adults with acute leukemia. Substantial changes occurred in the peripheral blood and bone marrow in the form of a decrease in white blood cells and blast cells and an increase in the platelet count and hemoglobin.

Although the data accumulated thus far is small, the consistency of the observations was worthy of presentation as a stimulus to further exploration of this mode of treatment.

Dosage Schedule

This combination chemotherapy regime consisted of 6-mercaptopurine in a dose of 2.5 mg. per kg. per day orally for five days, and on the sixth day cyclophosphamide was administered intravenously in a single dose of approximately 40 mg. per kg. Each course of therapy was repeated when the white blood cell count increased or blast cells reappeared. Prednisone was usually utilized concomitantly.

Results

The combination therapy of 6-mercaptopurine and cyclophosphamide was administered to ten patients with acute leukemia (Table 1). Two of the patients had chronic myeloid leukemia that was in an acute phase, three had subacute myeloid leukemia, and four had acute myeloid leukemia. One patient had an erythromegakaryocytic leukemia or a myeloproliferative syndrome.

In two patients (Cases 9 and 10) the cyclophosphamide was administered on the day of death or within a few days prior to death. One patient with subacute myeloid leukemia appeared to have an increase in the platelet count following the first course of combination therapy; but the development of a cerebral vascular episode on the basis of arteriosclerosis was a cause of discontinuance of leukemia therapy, and the patient died within two and one-half months of initiating treatment (Case 7).

Case Reports

Case 5

This 17-year-old boy had a two-month history of weakness. At the time of diagnosis, the white blood count was 26,300 with 41 per cent myeloblasts. The platelet count was 24,000 cmm. Bone marrow examination revealed 14 per cent myeloblasts, 2.6 per cent normoblasts, and decreased platelets. A diagnosis of subacute myeloid leukemia was established.

Because of the thrombocytopenia, two short courses of 6-mercaptopurine at 100 mg. a day for three days were administered with prednisone. The platelet count gradually decreased to 8,000 and the white blood count rose to 106,000. The hemoglobin decreased (Figure 1). Therefore, following four days of 6-mercaptopurine at 100 mg. a day, 2.75 gm. of cyclophosphamide was administered intravenously. There was a subsequent decrease in white blood count, a decrease in myeloblasts, an increase in hemoglobin, and an increase in platelets to normal ranges. At the end of five weeks, a repeat bone marrow examination revealed a hypoplastic marrow with a relative normoblastic hyperplasia. The normoblasts were 50 per cent and the myeloblasts 1.5 per cent; the platelets were normal. This remission lasted for three and one-half months.

At the time of the recurrence of the disease,

TABLE I
Data of Ten Patients Treated with 6-Mercaptopurine and Cyclophosphamide

				Duration (Months)					
Case No.	Sex	Age	Type of Myeloid Leukemia	Symptoms to Treatment	Treatment to Death	WBC Decreased	Myeloblasts Decreased	Hemoglobin Increased	Platelets Increased
1.	M	29	Acute	6.	2.	+	+	0	0
2.	F	52	Acute	1.	0.4	+	+	0	0
3.	M	70	Acute	0.3	2.3	+	+	0	0
4.	F	33	Acute	3.	9.	+	+	+	+
5.	M	17	Subacute	2.	10.	+	+	+	+
6.	F	67	Subacute	2.	1.	+	+	0	0
7.	F	63	Subacute	5.	2.5	+	—	0	?
8.	F	40	Chronic (acute phase)	69.	5.	+	+	+	+
9.	M	20	Chronic (acute phase)	8.	< .1	—	—	—	—
10.	F	70	Erythromegakaryocytic	24.	< .01	—	—	—	—

cyclophosphamide was administered without 6-mercaptopurine, followed by a decrease in the white blood count from 42,000 to 1,000 but no improvement in the platelet count. Two weeks later, a repeat course of 6-mercaptopurine and cyclophosphamide was administered with a decrease in the white blood count and improvement in the platelet count. This remission lasted two months. Subsequently the patient received repeated trials of therapy and expired ten months after the initial treatment. During this interval he received two courses with cyclophosphamide only, one course with 6-mercaptopurine only, one course with the combined therapy utilizing a low dose of cyclophosphamide, and two combination courses in which cyclophosphamide was administered in a dose of 2.75 gm. It was only with the latter combined regimen that an increase in the platelet count occurred.

Case 8

This 40-year-old woman was first known to have chronic myeloid leukemia in 1959. One year later, because of a white blood count of 40,000 and an iron deficiency anemia of 8.8 gm., ferrous sulfate was administered with an increase in the hemoglobin to normal ranges and a decrease in the white blood count to 12,000. This patient was followed for seven and one-half years from the onset of the disease. During the sixth year, an increase in the white blood count to 90,000 occurred and was followed by a spontaneous decrease to 40,000. Subsequently, because of the appearance of myeloblasts in the periphearal smear, 6-mercaptopurine was administered with a decrease in the total white blood count (Figure 2). Two and one-half months later, the disease reactivated and failed to respond to 6-mercaptopurine. Therefore 2 gm. of cyclophosphamide was administered with an abrupt drop in the white blood count and a disappearance of myeloblasts from the peripheral smear. This remission persisted for two and one-half months. Subsequently, the myeloblasts reappeared in the peripheral smear and disappeared following each course of combined 6-mercaptopurine and cyclophosphamide. Gradually, however, the platelet count decreased and death occurred from hemorrhage five months after the first course of combined 6-mercaptopurine and cyclophosphamide. The initial course of combined therapy produced a decrease in the total white blood count, a decrease in the blasts to zero, an increase in the hemoglobin, and an increase in the platelets.

Case 3

This 70-year-old man had acute myeloid leukemia. The white blood count was 250,000, of which 75 per cent were myeloblasts. The platelet count was reduced. The patient was acutely ill with thrombocytopenia and hemorrhage. Combination therapy produced an abrupt drop in the white blood count, myeloblasts, and platelets. Subsequently three other episodes of leukocytosis occurred with an increase in the myeloblasts. Combination therapy was followed by a decrease in the white blood count but not total disappearance of the myeloblasts. The dose of cyclophosphamide on the basis of body weight in this instance was not so great as in the other patients. The patient finally died of infection and hemorrhage 2.3 months later.

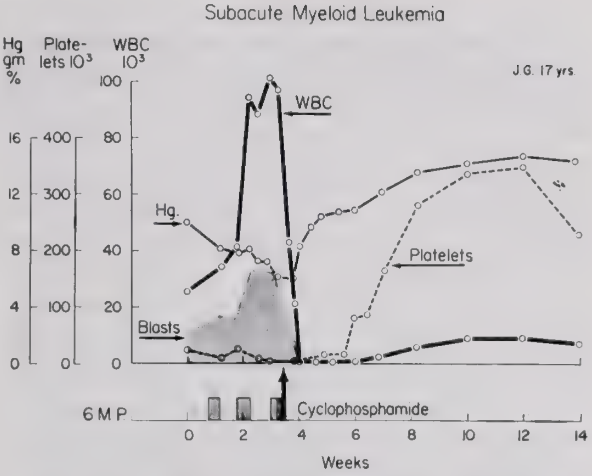

Fig. 1 — Case 5. Effect of combined therapy in a 17-year-old boy with subacute myeloid leukemia.

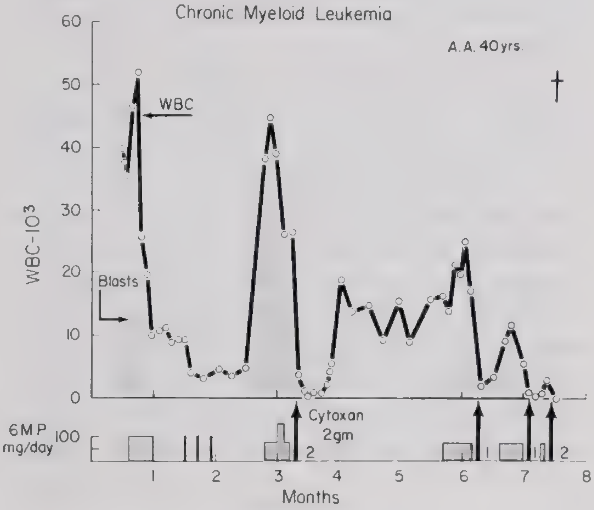

Fig. 2 — Case 8. Repeated courses of combined therapy evoked an antitumor effect.

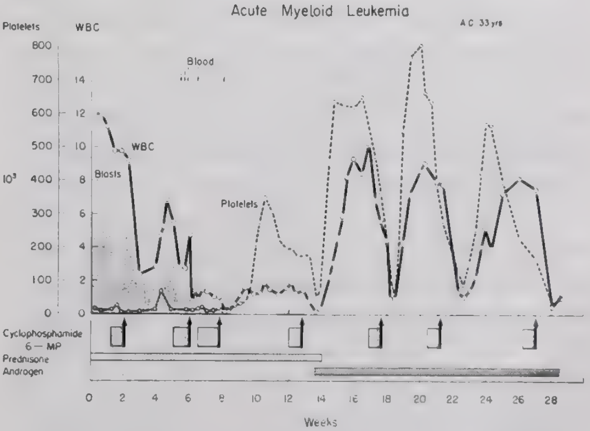

Fig. 3 — Case 4. Hematologic response to combined therapy in a patient with acute myeloid leukemia. The hemoglobin became normal.

Case 4

This 33-year-old woman had a three-month history of acute myelogenous leukemia which had been treated intensively with 6-mercaptopurine and prednisone. She was referred to the University Hospitals because of a lack of response to this therapy and the presence of thrombocytopenia. The total white blood count was 12,000 with 71 per cent myeloblasts. The platelet count was less than 20,000 per cmm. The patient was given a course of 6-mercaptopurine followed by cyclophosphamide, followed by an abrupt drop in the myeloblasts (Figure 3). Four weeks later, leukocytosis occurred and a second course of combined therapy was administered. Because of the persistence of blasts in the peripheral smear, a third course of therapy was given two weeks later. The white blood count decreased to levels below 1,000 cmm. and the platelets eventually increased to normal values. Testosterone enanthate 400 mg. three times a week intramuscularly was begun, and combined cytotoxic therapy was administered at monthly intervals with a gradual restoration of a normal hemoglobin and peripheral blood picture. Eight months after the initial course, the patient was asymptomatic with a complete bone marrow remission.

Of eight patients who received combination therapy for acute phases of myeloid leukemia, a decrease in total white blood count occurred in each instance. The hemoglobin rose in three patients and the myeloblasts decreased markedly in seven. A striking increase in thrombocytes occurred in three patients. A fourth patient may have demonstrated early evidence of this, but a cerebral vascular episode terminated the study. In two of the responding patients previous use of 6-mercaptopurine alone was not beneficial.

Discussion

Six-mercaptopurine has been utilized as a treatment of acute leukemia for more than ten years.[3] Cyclophosphamide has not been emphasized in the therapy of acute leukemia, although it has been used extensively in animal leukemias.[4] Hoogstraten reported the results of the Acute Leukemia Cooperative Group B with oral cyclophosphamide given at various dosage schedules,[5] but the drug was no better than placebos in prolonging survival and only slightly better than placebos in sustaining steroid induced remissions. The rate of administration seemed to make no difference; however, there was some suggestion that weekly doses were slightly more effective in maintaining remissions.

The rationale for combined chemotherapy has its foundation in the treatment of bacterial disease.[6] Studies on animal tumors have shown that the development of resistance to one chemotherapeutic agent may sometimes enhance susceptibility to another.[7] This is particularly true with the purine and folic acid antagonists. There is conclusive evidence that development of resistance to the purine analogs by bacteria and certain animal tumors is the result of enzymatic changes within the tumor cell. For 6-mercaptopurine resistance this change seems to involve a reduction in the amount of inosinic phosphorylase, thus providing a mechanism for the discovery of a synergistic drug.[8,9] Unfortunately this does not seem to be the mechanism of 6-mercaptopurine resistance in human leukemias. These findings have stimulated numerous trials with various combinations of agents. Six-mercaptopurine has been used in combination with methotrexate and azaserine,[10,11] but in both cases, the effect of the two drugs in combination was no greater than that expected for either of the two used separately.

In the present study, the short-term use of 6-mercaptopurine followed by a massive dose of cyclophosphamide produced a consistent decrease of white blood cells and myeloblasts. The most striking effect noted was the marked thrombocytosis which occurred in three patients. The platelet sparing effect of cyclophosphamide may be a factor in this phenomenon. A significant bone marrow remission occurred in two patients.

In two patients in whom massive androgen therapy was employed concomitantly with the cytotoxic therapy, a striking increase in hemoglobin occurred. This has been observed in the treatment of other conditions characterized by erythroid hypoplasia.[12] It would appear that sufficient leukemic elements of the marrow were destroyed to allow the normal cell precursors stimulated by the androgenic hormones to proliferate.

The action of cyclophosphamide is presumed to be similar to that of all the alkylating agents in that it destroys dividing cells more effectively than resting ones. The action of the alkylating agents on a cell involves a rather nonspecific effect due to the replacement of a hydrogen atom in a compound with an alkyl radical, with resultant denaturation of enzymes, chain rupture of nucleic acids, and cross-linking of DNA to itself and to its associated protein. The degree and type of damage is for the most part a function of the availability of the target. Like radiation, alkylating agents produce two types of cellular death.[13] The first is interphase death and results only when damage to the cellular proteins and nucleic acids has been extensive; a very high dose is required to kill a cell in this manner. The second type of death, mitotic death, occurs at a much lower dosage and is primarily due to damage to the chromosomes or the mitotic apparatus itself. This damage manifests itself at the time of division, but it may occur at any point in the cell cycle, although certain periods are more sensitive than others to injury. It is this second type of cell death that is utilized by both the radiotherapist and the chemotherapist. DNA and its associated proteins undergo rather marked alterations in their physiochemical state during the various stages of the cell cycle from the tightly clumped bands of chromatin in a mature nondividing cell to the filamentous, uncoiled strands of nucleoprotein in the primitive premitotic nucleus actively engaged in DNA synthesis. It is highly probable that the increased susceptibility to alkylating agents of cells engaged in premitotic DNA synthesis is a result of the increased availability of the uncoiled nucleoprotein for alkylation. Tissue sensitivity, in turn, is largely a function of the per cent of sensitive cells present; indeed, the mitotic index is generally accepted as an indicator of tissue sensitivity to alkylating agents. Any increase, therefore, in the per cent of sensitive cells in a tissue would be expected to result in an increase in the sensitivity of that tissue to alkylating agents.

Although 6-mercaptopurine is not incorporated into nucleic acids[9,14,15] it inhibits nucleic acid synthesis because of its metabolism through the usual pathways for anabolism and catabolism of the purine bases. It has been shown to inhibit at least four reactions: (1) the conversion of phosphoribosylpyrophosphate to 5-phosphoribosylamine; (2) the conversion of inosinic acid to adenylosuccinate; (3) the conversion of adenylosuccinate to adenylic acil; and (4) the conversion of inosinic acid to xanthylic acid.[16] These reactions are involved in the de novo synthesis of the purine bases, and when they are inhibited, the synthesis of nucleic acid is impaired unless the cell develops the capacity to depend exclusively on the salvage pathways as a source of preformed purines. This latter phenomenon has been observed in 6-mercaptopurine-resistant cells.[16] That 6-mercaptopurine may result in inhibition of DNA synthesis is evidenced clinically by the development of a megaloblastic bone marrow.[17] Treatment with 6-mercaptopurine would therefore be expected to produce a shift in the cell population of the bone marrow in such a way as to produce an increase in the per cent of cells in that stage of the cell cycle which has an increased sensitivity to alkylating agents. Pretreatment with 6-mercaptopurine, therefore, would be expected to greatly enhance the sensitivity of a cell population to cyclophosphamide.

Summary

Ten adults with acute myeloid leukemia were treated with combination therapy using a short course of 6-mercaptopurine and a massive dose of cyclophosphamide. There was a consistent reduction in white blood cells and myeloblasts. A marked thrombocytosis and an increase in hemoglobin were observed in three patients. A possible mechanism for the synergism of these two drugs is the ability of the 6-mercaptopurine to provide the alkylating agent with an increased number of susceptible cells.

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2. Roath, S., Israëls, M. C. G., and Wilkinson, J. F.: The Acute Leukemias: A Study of 580 Patients. Quart J Med 33:257, 1964.

3-17 May be secured from the author or the reprints.

The Sarsaparilla Era

Sarsaparilla is a medicinal preparation made from the root of smilax. Early in the nineteenth century a German physician thought that he had found it to be very valuable as a tonic and alterative. . . . On the strength of these clinical observations, physicians all over the world used sarsaparilla very commonly. It was sufficiently bitter and mediciny in flavor, as a rule, to make people realize that they were taking medicine, and many of them proceeded to get better, and most of them attributed their betterment to the sarsaparilla, but medical experience showed that there was no good reason to think so.

These sarsaparilla preparations were widely advertised. Every drug store in the country carried them in stock, but after a time so did every grocery store. There were literally millions of people in this country who swore by sarsaparilla. Many of them were quite sure that they had been sinking into an early grave and sarsaparilla had just taken them by the hand and lifted them up and given them renewed vigor, restored their appetite, regulated their bowels and given them back health and strength, and they were perfectly willing to tell all the world so.

The sarsaparillas had a wonderful effect upon the mind. The active ingredient in them was not the medicine on the inside of the bottle, but the printer's ink on the outside, and the still larger amount of printer's ink that was administered through the eyes of readers of the newspapers, the special advertising literature, the almanacs and the like which were issued, and the testimonials which were distributed. Great was sarsaparilla and great was its vogue, and now it is no more; only the memory of it remains, oh yes! and the fortunes that were made in its distribution, while sterling philanthropists took on themselves the task of doing the world good.*

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*Walsh, James: Cures, D. Appleton & Co., 1924.

Oliver Wendell Holmes on Drugs

Throw out* opium, which the Creator himself seems to prescribe, for we often see the scarlet poppy growing in the cornfields, as if it were foreseen that wherever there is hunger to be fed there must also be pain to be soothed; throw out* a few specifics which our art did not discover; . . . throw out* wine, which is a food, and the vapors which produce the miracle of anesthesia — and I firmly believe that if the whole *materia medica,* as now used, could be sunk to the bottom of the sea, it would be all the better for mankind — and all the worse for the fishes.

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*By "throw out" Holmes meant "except."

Watch It!

A snack is defined as the pause that refleshes. — Fredonia (Kan.) Herald.

Pulmonary Nocardiosis*

Report of Two Cases

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NOCARDIOSIS IS USUALLY a chronic, suppurative disease, but occasionally it runs an acute, fatal, fulminating course, manifesting itself by the involvement of the lungs, skin, brain, and other organs. The Nocardia organism is one of the soil-inhabiting Actinomycetaceae. There are at least 33 species; however, the most common pathogenic species, and the one usually responsible for nocardiosis in man, is Nocardia asteroides. The rare mycotic infection, caused by Nocardia, was first described in 1888 by Nocard,[1] who isolated the organism from cattle with farcy, and in 1890 by Eppinger,[2] who reported the first case of Nocardia meningitis.

Case Reports

Case 1

This 72-year-old white male, paraplegic for most of his life from undetermined cause, first noted cough, shortness of breath, and fever in June 1965. His chest film showed a pneumonic lesion in the upper lobe of the right lung which did not respond to treatment with penicillin. A subsequent film indicated a spread of his lesion with cavity formation.

He was admitted to Glen Lake State Sanatorium on August 2, 1965, because of suspected tuberculosis. Following admission he remained febrile with a temperature of 101° to 102°. His hemoglobin was 10 gm. and white blood cell count 27,000, with 86 per cent neutrophils. Skin tests, including tuberculin and histoplasmin and coccidioidin were negative. Sputum smears and cultures were negative for acid-fast bacilli and pathogenic fungi, but Candida and Staphylococci were present. A fluctuant mass, noted as a tumor, was found in his left anterior thigh.

The patient was treated with penicillin, streptomycin, chloromycetin, and ampicillin but showed no clinical response. Lumbar puncture was performed because he appeared semistuporous and showed signs of meningeal irritation; the spinal fluid revealed 1,700 cells, of which the great majority were polymorphonuclear leukocytes. Cultures of spinal fluid showed no growth of acid-fast bacilli, fungi, or other organisms. Gross hematuria appeared, but urine cultures grew only Candida and Pseudomonas aeruginosa. The fluctuant mass in the left anterior thigh was aspirated and a culture of the aspirated yellow pus grew Nocardia asteroides.

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Treatment with sulfadiazine, 12 gm. daily for two days, and then 6 gm. daily in divided doses, combined with tetracycline and mycostatin, began on August 30. Blood and spinal fluid levels of sulfadiazine were determined and showed the blood level to be 23 mg. per cent and the spinal fluid level, 13 mg. per cent. The patient's course slowly deteriorated, with progression of both cerebral and pulmonary conditions, until his death on September 9, 1965.

Autopsy disclosed Nocardia asteroides forming multiple, focal abscesses in the lungs, brain, right kidney, and subcutaneous tissue. Nocardia asteroides organisms were abundant in the involved tissue and demonstrated by culture. The brain showed a paraventricular white mass and some plaquing of gray matter, possibly due to multiple sclerosis.

Comment

This case illustrates the acute, fulminating nature of this disease. The diagnosis and treatment were perhaps instituted too late to alter the course. When there is cerebral involvement, the treatment becomes more difficult. It is interesting to note that repeated cultures of sputum, urine, and spinal fluid for fungi were negative. The pneumonic lesion with abscess not responding to intensive antibiotics and the subsequent involvement of brain and skin (subcutaneous abscess) led to suspicion of this rare disease.

Case 2

This 25-year-old Indian housewife was transferred from the Hennepin County General Hospital to Glen Lake State Sanatorium on June 24, 1952, with a history of good health until approximately one month before admission. At this time she experienced a sudden onset of sharp, pleuritic pain in the lower chest, associated with night sweats and a 12-pound weight loss. A roentgenogram made at General Hospital showed an extensive pneumonic type of infiltration of the upper lobe of the left lung suggestive of tuberculosis. Two sputum smears were positive for acid-fast bacilli, although cultures of the same specimens were negative. She was immediately put on a daily regimen of 1 gm. streptomycin sulfate and 12 gm. para-amino-salicylic acid.

On admission to the sanatorium she was found to have numerous small, shotty, nontender movable nodes in the anterior and posterior triangles of both sides of the neck. Skin tests were positive to old tuberculin (10 tuberculin units) and histoplasmin, but negative to coccidioidin and blastomycin. Laboratory study showed the hemoglobin to be 12.4 gm. and white blood cell count 10,150 with neutrophils, 81 per cent; lymphocytes, 9 per cent; monocytes, 1 per cent; eosinophils, 8 per cent; and basophils, 1 per cent. Sputum cultures were negative for acid-fast bacilli. Her chemotherapy, consisting of streptomycin and para-amino-salicylic acid, was continued.

By September her cervical glands began to enlarge and became painful and tender, and on September 15 a large cervical node was removed, which, on microscopic section, showed extensive necrosis. No tubercle bacilli were found by smears or cultures, but a fungus culture revealed growth of Nocardia asteroides. Bronchoscopy on December 31 showed a definite, ulcerative bronchitis involving the left main and lower lobe bronchi. The posterior and apical segments of the upper lobe of the left lung were removed on July 25. Microscopic section showed chronic, granulomatous inflammation with a necrotic area surrounded by fibrous tissue, some scattered giant cells, and one cluster of epithelioid cells. Tubercle bacilli and fungi were not found by culture or by guinea-pig inoculation. The patient deserted the sanatorium on February 24, 1954, and no follow-up information has since been available.

Comment

In this case Nocardia asteroides was cultured from the excised cervical lymph node. The pulmonary lesion may have been caused by Nocardia infection, although culture of sputum was negative for Nocardia. Because of the acid-fast property of Nocardia, this disease is often misdiagnosed as tuberculosis; however, coexistence of both diseases is possible. This patient recovered from this disease after treatment with pulmonary resection, excision of cervical glands, and chemotherapy for tuberculosis.

Discussion

Both Nocardia and Actinomyces belong to the soil-inhabiting Actinomycetaceae.[3] Nocardia is aerobic,* gram-positive, delicate, branching, and filamentous; some species are acid-fast and may be confused with tubercle bacilli. The filaments are seldom, if ever, visible with the hematoxylin and eosin stain but are easily visible with the Giemsa stain or one of the modifications of the gram stain. Nocardia grows slowly on all common laboratory media and should be differentiated from tubercle bacilli and Actinomyces.

Peabody and Seabury[4] pointed out that the recovery of this organism sometimes is most difficult to interpret; an occasional colony may occur as a contaminant or saprophyte; but numerous colonies or repeated isolations of the organisms are more significant. Demonstration of this organism in tissue, by cultural and histologic methods, is positive evidence of this disease. Nocardiosis is usually considered to be an exogenous infection; is caused by a fungus present in the soil; and has an incidence evenly distributed over the world, with no racial preference, but higher in men than in women. Preponderance of pulmonary involvement suggests that the respiratory tract is the portal of entry. Nocardiosis has occurred following dental extraction, and the alimentary tract as a portal of entry has also been emphasized.[5,6]

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*See Test Your Word Score Page 1107.

The clinical and radiologic features are variable and nonspecific and may resemble those of tuberculosis, pneumonia, lung abscess, mycotic infections, and other conditions. The main clinical signs and symptoms are cough, yellow sputum, fever, night sweats, and pulmonary consolidation or abscess. Radiologic features are the dense areas of lobular or lobar consolidation and areas of rarefaction resembling lung abscess, with or without pleural reaction. The pathologic process takes the form of abscesses in the lungs, brain, lymph nodes, skin (subcutaneous tissue), and other sites. The primary site is frequently in the lungs. The histologic picture is that of extensive necrosis of tissue with a marked surrounding cellular reaction but no fibroblastic reaction.

Diagnosis

Although the organisms can be identified easily with proper stains, the diagnosis of nocardiosis cannot be made by histologic examination alone. The demonstration of the organism by culture from proper materials and tissue is the only confirmative laboratory procedure. The differential diagnosis includes: tuberculosis; mycotic infections, such as histoplasmosis, blastomycosis and actinomycosis; bronchogenic carcinoma, especially with intracerebral metastasis; bacterial pneumonia; lung abscess; and others. Coexistence of this disease with others or this disease superimposed upon other grave diseases is a distinct possibility. When acute pneumonia or subacute pneumonia does not respond to regular antibiotic therapy and progresses to lung abscess and meningeal involvement, nocardiosis should be suspected.

Treatment

Treatment is chiefly medical, but may be supplemented by drainage and excision of abscess or empyema. Sulfadiazine, given in divided doses of 4 to 6 gm. daily, remains the drug of choice.[7-9] Nocardiosis can be treated and controlled; therefore, early recognition is of paramount importance. Early administration of a specific antibiotic may be lifesaving and may prevent the spread of the organisms to the central nervous system with the subsequent crippling effects. With prompt diagnosis, prognosis is good; but fulminating cases with brain abscess or cases in which nocardiosis is superimposed upon another grave disease have a very poor outlook. The Nocardia organism should be tested to determine sensitivity to sulfadiazine as well as to other broad-spectrum antibiotics. Peabody and Seabury[10] suggested the daily use of 4 gm. of sulfadiazine and 2 gm. of a broad-spectrum antibiotic. Treatment should continue for several months after clinical manifestations have cleared, before the patient is considered cured.

Summary

This is a report of two cases of pulmonary nocardiosis, emphasizing the importance of early recognition of this treatable infection. Nocardiosis is usually a chronic, suppurative disease, but occasionally it runs an acute, fulminating course. The primary infection is usually in the lungs, with metastatic lesions to the brain, skin, (subcutaneous tissue), and other sites. It is caused, in almost all cases, by Nocardia asteroides. Pneumonic processes which do not respond to antibiotics and which progress to abscesses or spread to the central nervous system should suggest this rare disease. Prognosis is favorable, provided diagnosis is early and specific treatment is begun. Treatment is mainly medical, with sulfadiazine as the drug of choice. Surgical treatment consists of drainage or excision of abscesses.

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2-10 May be secured from the author or the reprints.

Gulliver's Travels — Jonathan Swift*

Gulliver — On the Virtues of Living in an Island Without Man

Gulliver had now lived for five years on the island where the horse was the master and found the experience very gratifying.

"No man could more verify the truth of these two maxims: that nature is very easily satisfied; and, that necessity is the mother of invention. I enjoyed perfect health of body and tranquillity of mind; I did not feel the treachery or inconstancy of a friend, nor the injuries of a secret or open enemy. I had no occasion of bribing, flattering or pimping, to procure the favor of any great man, or of his minion. Here was neither physician to destroy my body nor lawyer to ruin my fortune; no informer to watch my words and actions, or forge accusations against me for hire; here were no jibers, censurers, backbiters, pick-pockets, highwaymen, house-breakers, attorneys, bawds, buffoons, gamesters, politicians, wits, spleneticks, tedious talkers, controvertists, ravishers, murderers, robbers, virtuosos; no dungeon, axes, gibbets, whipping posts or pillories; no cheating shop-keepers or mechanics; no pride, vanity or affectation; no fops, bullies, drunkards, strolling whores, or poxes; no ranting, lewd, expensive wives; no stupid, proud pedants; no importunate, over-bearing, quarrelsome, noisy, roaring, empty, conceited, swearing companions; no scoundrels raised from the dust upon the merit of their vices; or nobility thrown into it on account of their virtues; no lords, fiddlers, judges, or dancing masters."

— Heritage Press 1940

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*See Minnesota Med 49:850, 1966.

The Autopsy of Samuel Johnson

On opening into the cavity of the chest, the lungs did not collapse as they usually do when air is admitted, but remained distended, as if they had lost the power of contraction; the air-cells on the surface of the lungs were also very enlarged; the right lobe adhered very strongly to the diaphragm; the internal surface of the trachea was somewhat inflamed; no water was found in the cavity of the thorax. The heart was exceedingly large and strong, the valves of the aorta were beginning to ossify; no more fluid than was common was contained in the pericardium. In the abdomen seemed to be incipient peritoneal inflammation and ascites; the liver and spleen were firm and hard; the spleen had almost the feel of cartilage. A gall stone about the size of a pigeon's egg was taken out of the gall bladder; the omentum was exceedingly fat; nothing remarkable was found in the stomach; the folds of the jejunum adhered in several places to one another; there was also a strong adhesion by a long slip between the colon and bladder; the pancreas was remarkably enlarged; the kidney of the left side tolerably good, some hydatids beginning to form on its surface; that of the right side was almost entirely destroyed, and two large hydatids formed in its place. (Dr. Johnson never complained of any pain in this part; the left testicle was perfectly sound in structure, but had also a number of hydatids on its surface, containing a fatty gelatinous fluid, the right testicle had hydatids likewise, but the spermatic vein belonging to it was exceedingly enlarged and varicose.) The cranium was not opened.

— James Wilson (1725-1821)

Erythroblastosis Fetalis

Management at the University of Minnesota Hospitals

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MUCH PROGRESS in the clarification of the etiology and pathophysiology of erythroblastosis fetalis has been made in relatively recent years. Although various forms of the disease — hydrops fetalis, icterus gravis neonatorum and hemolytic anemia of the newborn — have been known for a long time,[1] it was not until 1932 that these conditions were shown to be the result of the same disease.[2] In 1940 Landsteiner and Weiner[3] reported the discovery of the Rh antigen; its importance in the etiology of erythroblastosis fetalis was emphasized by Levine et al.[4] one year later.

It has been well established that the transplacental passage of fetal erythrocytes occurs commonly during normal pregnancy. The number of such erythrocytes present in the maternal circulation during pregnancy is increased in some complications such as abruptio placentae and toxemia, as well as a result of operative obstetric procedures such as cesarean section, forceps delivery and manual removal of the placenta.[5,6] However, there is no unanimity of opinion concerning this problem.[7]

Rh antibodies of small molecular size formed in the mother readily pass the placenta to the fetus and attach to the Rh substance of fetal erythrocytes. The life span of these affected erythrocytes is decreased by hemolysis from a normal of 100 to 200 days to approximately 10 days. The fetus may or may not successfully combat the resultant anemia, although the excess bilirubin released by the hemolysis is efficiently excreted through the placenta.

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Clinical Management

The clinical problem is one of management of the affected infant. At the present time there is no available method of preventing maternal sensitization, although very promising studies are in progress.[8,9] Attempts at destruction or modification of the antibodies have been unsuccessful. Methods for increasing the capacity of the fetus to produce erythrocytes are not yet available.

Timing of Delivery

Selection of patients and proper timing of delivery will result in improved over-all results. Premature delivery is fraught with hazard; but a compromise in fetal maturity may be necessary as the severity of the hemolytic disease increases. Premature delivery of an unaffected or mildly affected infant that does not survive is tragic, but equally tragic is the loss of a mature infant with erythroblastosis fetalis who might have survived with earlier delivery and exchange transfusion. The major obstacle in early delivery has been the inability to predict the severity of the fetal disease.

The management of the Rh negative patient is based on careful evaluation during pregnancy. Rh antibodies must be detected if present. Once a patient is known to be immunized, the status of the fetus in utero must be evaluated. The fetus may be Rh compatible and not affected or may be Rh positive and have hemolytic disease. In the latter situation the severity of the disease must also be assessed.

The methods commonly used to evaluate a current pregnancy are the past obstetrical and transfusion history, the antibody titers, the present prenatal course, and the husband's Rh zygosity.

The Husband's Genotype

Determination of the husband's genotype is of obvious value. Although the probability of the Rh positive husband's heterozygosity can be estimated, it cannot be serologically proven, because the anti-d (Hr^o) antigen is not available. An Rh negative child or parent confirms the husband's heterozygosity but is of no value in assessing the severity of hemolytic disease of the Rh positive fetus in utero.

Impending Fetal Death

Occasionally there are indications during the prenatal course that fetal demise is impending. A sudden decrease in fetal movement or the "toxemia syndrome," characterized by edema, rapid weight gain, hypertension, proteinuria and generalized pruritus may occur. Unfortunately by this time the fetus is usually hydropic and salvage is rarely possible.

Spectrophotometry

Because the evaluation of the status of the fetus in utero by history of previous pregnancies and the level of maternal antibody titers in the current pregnancy were not always reliable, Bevis[10] pioneered the study of the composition of amniotic fluid and in 1956 introduced the spectrophotometric analysis of amniotic fluid. He utilized the information obtained from these studies to estimate the degree of fetal affectation prior to delivery. In 1961 Liley[11] reported his method of evaluating the spectral absorption curve of amniotic fluid. Using logarithmic* values, he plotted the optical density of the additional absorption at 450 millimicrons on the ordinate and the duration of gestation on the abscissa of a graph. On this graph zones were delineated which corresponded to the degree of fetal disease. Serial amniotic fluid examinations resulted in improved evaluation of the degree of fetal hemolytic disease. This technique is now widely used and its value is established.

Present Report

In order to correlate some of these factors

TABLE I
RH ISO-Immunization

Infants with Erythroblastosis Fetalis due to RH incompatibility	100
A. Mild — no treatment required	29
B. Moderate — one exchange transfuion	22
C. Severe — two or more exchange transfusions	28
D. Hydrops fetalis, liveborn	6
E. Fetal death in utero	15

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*See Test Your Word Score Page 1107.

with the fetal outcome the records of Rh negative patients delivered at the University of Minnesota Hospitals from January 1956 to April 1965 have been reviewed. Of approximately 800 Rh negative patients who were delivered, 104 (13%) had serum with Rh antibodies. Five of these patients were sensitized by blood administration prior to pregnancy. Nineteen (18.2%) delivered one or more Rh compatible infants.

The Sensitized Mothers

The 104 sensitized patients delivered a total of 131 infants. Twenty-two infants were Rh compatible, and nine were Rh incompatible but did not have hemolytic disease, as the cord blood direct Coombs test was negative. The latter group is difficult to explain, but the avidity of Rh antibodies for the antigen varies, particularly when the titer is low.[12] The Coombs test could have been so weakly positive that it was not detectable. Laboratory error cannot be completely excluded. One hundred infants (76.3%) were Rh incompatible and had erythroblastosis fetalis. The severity of the disease among these infants is shown in Table 1. Three of the fetal deaths in utero were associated with fibrinogenopenia of clinical significance.

The Iso-immune Infants

The over-all results of the 131 infants delivered of Rh sensitized patients are seen in Table 2. The perinatal* mortality rate of the 100 infants with erythroblastosis fetalis was 26%. Of the 27 infants who did not survive, 21 died in utero from the disease or were hydropic and unsalvageable at birth. This finding demonstrates dramatically the need to determine the severity of the hemolytic disease in utero if increased salvage of these infants by intrauterine transfusion and/or early delivery prior to the development of hydrops is to be accomplished. Intrauterine fetal transfusion, as first described by Liley,[13] may be necessary one or more times to enable some fetuses to survive and mature sufficiently to decrease the risk inherent to early delivery.

Previous Pregnancies

The outcome of previous pregnancies has been shown to be an important factor in estimating the outcome of a current pregnancy[14] (Table 3). Of those patients who bore infants with the severest form of the disease in a previous pregnancy (fetal death in utero) three delivered Rh compatible infants, six delivered infants with mild or moderate disease, three delivered infants with severe disease, and nine delivered hydropic or stillborn infants. Of the 57 patients who had not previously delivered an infant with erythroblastosis fetalis, 10 delivered infants with severe disease and only four experienced fetal death in utero.

Rh Antibody Titer

The level of the maternal Rh antibody titer is also used to estimate fetal prognosis. The outcome of the first pregnancy in which an indirect Coombs antibody titer was dem-

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*See Test Your Word Score Page 1107.

TABLE 2
RH ISO-Immunization
Erythroblastosis Fetalis (E.F.) and Infant Survival

Infants	Total	Neonatal Death	Stillborn	Perinatal Mortality
A. RH compatible	22	1	0	4.5%
B. RH incompatible, no E.F.	9	0	0	0
C. RH incompatible with E.F.	100	11	15	26.0%
1. Mild E.F.	29	0	0	0
2. Moderate E.F.	22	2	0	9.0%
3. Severe E.F.	28	3	0	10.3%
4. Hydrops fetalis, liveborn	6	6	0	100%
5. Fetal death in utero	15	0	15	100%
D. All infants delivered by RH ISO-Immunized patients	131	12	15	20.6%

onstrated is correlated with the highest maternal titer in that pregnancy (Table 4). Although there is a definite trend toward more severely affected infants among patients with higher titers, a number of less severely affected infants were delivered when the titers were high. There was no severely affected infant when the highest titer was 1:16 or less and only one when the titer was 1:32. The trend of serial antibody titers in the first sensitized pregnancy is therefore of some value. The correlation between severity of the hemolytic disease in the infant and the height of the titer when antibodies had been demonstrated in preceding pregnancies is presented in Table 5. Although the same trend is seen, it is of less prognostic value when compared to the titer level in the first demonstrably sensitized pregnancy.

Method of Delivery

One hundred eighteen infants were delivered vaginally. Seventy-two of these were delivered after the spontaneous onset of labor and 12 (16.6%) did not survive. Labor was induced in 46 instances with nine (19.5%) perinatal deaths. Of these 21 infants that did not survive, 15 were dead in utero and three were hydropic at birth. Only three of the 43 moderately or severely affected infants were lost after vaginal delivery. Cesarean section was performed on 13 occasions with erythroblastosis fetalis as the sole indication. Although five of these infants did not survive, three were known to be hydropic, and operation was performed in an heroic attempt to salvage the infants. One Rh negative infant weighing 2125 grams was delivered by cesarean section at 35 weeks' gestation and died of respiratory distress syndrome. The mother of this infant had previously delivered three stillborn infants. Although amniotic fluid studies had been performed, they wrongfully suggested severe affectation. The correlation between survival, severity of the disease, and the mode of delivery is presented in Table 6.

Nineteen patients in the series were admitted for delivery who were not registered in the prenatal clinic and 12 of their infants did not survive.

The Birth Weight

The birth weight of the infants is of great significance as related to survival. Nine infants were delivered who weighed less than 1500 grams and none survived. Four infants weighed between 1500 and 2000 grams. Two of these infants with hemolytic disease survived but neither required exchange transfusion. Of 16 infants who weighed from 2000 to 2500 grams five were hydropic or stillborn. Ten infants survived following one or more exchange transfusions. The last was the 2125-gram Rh negative infant previously discussed. Of 102 infants that weighed more

TABLE 3
RH ISO-Immunization
Infant Survival and Outcome of Most Severely Affected Preceding Pregnancy

Infant of Studied Pregnancy	Preceding Pregnancies							
	No E.F.	No E.F. Blood*	E.F. Recovered	E.F. Kernicterus	E.F. N.N.D.	E.F. Hydrops	E.F. F.D.I.U.	Total
RH compatible	6	1	7	0	1	4	3	22
RH incompatible								
No Disease	7	1	1	0	0	0	0	9
Mild E.F.	19	0	7	1	0	0	2	29
Moderate E.F.	11	0	5	0	2	0	4	22
Severe E.F.	10	3	10	1	0	1	3	28
Hydrops, liveborn	0	0	1	1	0	0	4	6
Fetal death in utero	4	0	2	0	4	0	5	15
Total	57	5	33	3	7	5	21	131

*Sensitized by RH Incompatible Blood Administration (E.F., erythroblastosis fetalis; N.N.D., neonatal death; F.D.I.U., fetal death in utero) than 2500 grams, 10 did not survive. Five of these were stillborn and one was liveborn but hydropic and did not survive. The other four died of severe hemolytic disease despite one or more exchange transfusions.

Duration of Gestation

Of interest is the duration of gestation at the time of delivery or fetal death in utero of the 21 infants who were stillborn or liveborn with hydrops fetalis. These findings together with the registered or unregistered status of the mother are presented in Table 7. Eleven patients with fetal death in utero had not been registered in the prenatal clinic of the University of Minnesota Hospitals. One registered patient with fetal death in utero at 36 weeks' gestation had abruptio placentae and toxemia. The infant was not hydropic. Two other registered patients had delivered stillborn infants weighing 2080 and 2205 grams. Fetal death occurred in one patient prior to 24 weeks' gestation.

All the patients who delivered liveborn hydropic infants were registered. Four of these infants weighed under 2000 grams, one weighed 2400 and another 2500 grams. Cesarean section was performed on three of the patients after 31 weeks' gestation and labor was induced in one patient.

It appears from this table that among the registered patients, two of the infants that died in utero and all of the six hydropic infants might have been salvaged at the present time with intrauterine fetal transfusion.

Sensitization to Rh factors other than

TABLE 4
RH ISO-Immunization
Severity of Disease and Antibody Titer (Indirect Coombs)
First Pregnancy with Demonstrable Antibodies

Severity of Disease	Highest Maternal Titer: Unknown	1-8 or Less	1-16	1-32	1-64	1-128	1-256 and Over
RH compatible	0	5	0	1	0	0	1
RH incompatible							
No disease	0	7	1	0	0	0	0
Mild E.F.	1	10	1	2	1	2	2
Moderate E.F.	2	1	1	4	0	1	2
Severe E.F.	0	0	0	1	2	3	7
Hydrops, liveborn	0	0	0	0	0	0	0
Fetal death in utero	0	0	0	0	1	0	3
Total	3	23	3	8	4	6	15

TABLE 5
RH ISO-Immunization
Severity of Disease and Antibody Titer (Indirect Coombs)
Pregnancies Subsequent to the First with Demonstrable Antibodies

Severity of Disease	Highest Maternal Titer: Unknown	1-8 or Less	1-16	1-32	1-64	1-128	1-256 and Over
RH compatible	0	2	0	2	2	1	8
RH incompatible							
No disease	0	1	0	0	0	0	0
Mild E.F.	0	1	2	3	0	2	2
Moderate E.F.	1	1	0	0	2	1	6
Severe E.F.	1	1	0	0	1	2	10
Hydrops, liveborn	0	0	0	0	0	0	6
Fetal death in utero	1	0	0	2	1	1	6
Total	3	6	2	7	6	7	38

D (Rh°) occurred in nine patients, although anti-D was also present in four. When sensitization to two or more factors was present, the anti-D sensitization was probably the more significant (Table 8). Of significance is the fact that three patients were D(Rh°) positive but were sensitized to c (hr′). These patients delivered seven infants who were acutely ill. This experience demonstrates the need for additional screening to identify the less common antibodies in the Rh positive patient if an obstetrical history indicates that a previous infant developed neonatal jaundice.

Amniotic Fluid Evaluation

Studies of amniotic fluid pigment are now commonly utilized to evaluate the severity of fetal hemolytic disease. Transabdominal amniocentesis to obtain fluid for analysis is indicated when the maternal antibody titer is 1:32 or greater. Although this procedure is usually performed at 31 or 32 weeks' gestation it may be done as early as 24 weeks when fetal death in utero has occurred in a previous pregnancy. Subsequent amniotic fluid samples are drawn at two to three-week intervals and determinations made to establish a trend in the height of the peak at a wavelength of 450 millicrons due to "bilirubinoid" pigments.

Technique

Transabdominal amniocentesis is not a difficult procedure but should be done with sterile technique. The patient's bladder should be empty and the fetal position determined. The site of the puncture in the region of the fetal small parts one or two inches from the midline is injected with a local anesthetic solution. A five to eight-inch 20-gauge needle with a stylet is introduced

TABLE 6
RH ISO-Immunization
Severity of Disease and Type of Delivery

	Vaginal Delivery						
	Spontaneous Labor		Induced Labor		Cesarean Section		
Severity of Disease	Number	Deaths	Number	Deaths	Number	Deaths	Total
RH compatible	10	0	10	0	2	1	22
RH incompatible							
No disease	9	0	0	0	0	0	9
Mild E.F.	17	0	11	0	1	0	29
Moderate E.F.	13	0	6	1	3	0	22
Severe E.F.	12	1	12	1	4	1	28
Hydrops, liveborn	2	2	1	1	3	3	6
Fetal death in utero	9	9	6	6	0	0	15
Total	72	12	46	9	13	5	131

TABLE 7
Erythroblastosis Fetalis
Time of Fetal Death

	Time of Fetal Death and Delivery in Weeks of Gestation								
	Under 24	24-26	27-28	29-30	31-32	33-34	35-36	Over 36	Totals
Fetal Death In Utero									
Registered	1	0	0	0	1	1	0	1	4
Unregistered	2	0	1	3	0	2	2	1	11
Hydrops Fetalis									
Registered	0	0	1	1	2	1	1	0	6
Unregistered	0	0	0	0	0	0	0	0	0
Totals	3	0	2	4	3	4	3	2	21

through the abdominal and uterine walls. The placenta should be avoided if possible. Approximately 10 milliliters of amniotic fluid is withdrawn and transferred to a sterile tube. The fluid should be protected from light and ideally should not be contaminated with blood. It should be centrifuged within two hours or immediately if it contains blood. The supernatant fluid should be filtered using Whatman No. 5 or S & S 597 filter paper. It can be stored at room temperature and sent in the mail for analysis if necessary.

Complications

Amniocentesis fails in about 5 to 10% of the attempts. Blood is obtained in almost 50%.[15] When blood is obtained, an Rh determination and direct Coombs test are performed. Fetal erythrocytes are identified by the acid elution technique.[5] At least 10 days should be allowed after a bloody tap before amniocentesis is repeated. Serum, especially that from an affected fetus, will enlarge the optical density peak at 450 millimicrons. Meconium is rarely encountered early in gestation but when present has a slightly different absorption wave length. The injection of a radio-opaque medium and a dye aid in obtaining fluid from each amniotic sac in a twin pregnancy.[16] Intestinal atresia and anencephaly increase the bilirubin content of amniotic fluid.[17]

Occasional complications of amniocentesis have been reported. Amnionitis has been encountered by Liley.[21] Fairweather[15] noted episodes of hyperpyrexia in his patients, the etiology of which was not determined. Premature delivery may occasionally follow amniocentesis. An increase in antibody titer following amniocentesis has been reported.[18,19] This is due to disruption of the fetal-maternal placental circulation but ordinarily does not affect the prognosis for the fetus or for infants of subsequent pregnancies.[20] Nevertheless, amniocentesis should not be performed without sufficient indication.

Case Reports

Two case reports are presented to demonstrate the value of amniotic fluid findings in the management of individual patients with Rh isoimmunization.

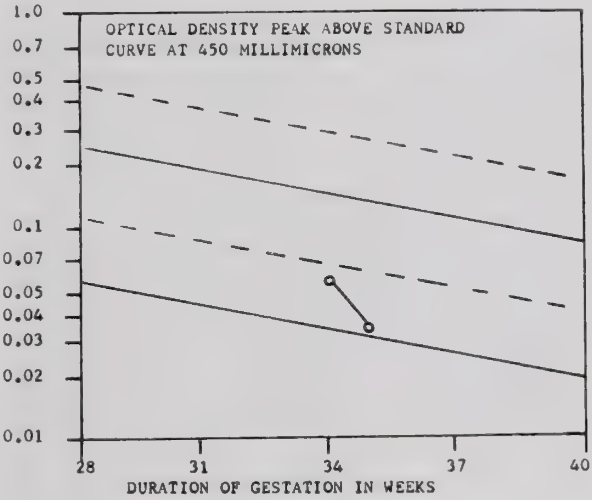

Fig. 1
Amniocentesis at 34 and 35 weeks' gestation. Pitocin induction of labor at 37 weeks. Infant — 3425 grams, blood group AB, CDe/c; direct Coombs +. Cord blood — HGB 15.1 gm%, bilirubin 5.7 mg%. Three exchange transfusions. Highest serum bilirubin 26.3 mg% on third day.

TABLE 8
RH ISO-Immunization
Sensitization to Factors Other Than D (RH_0)

		Severity of Disease				
RH Factors	Patients	RH Negative	Mild	Moderate	Severe	Hydrops Fetalis
D, C, E (Rh_0, rh′, rh″)	1	1	0	0	0	0
c (hr′)	3	0	0	4	2	1
E (rh″)	1	0	2	0	0	0
D, C (Rh_0, rh′)	3	0	0	1	2	0
e (hr″)	1	0	1	0	0	0

Case 1

A 42-year-old para 5-0-0-5 patient was blood group A, cde. Her husband was blood group B, CDE. Her first four infants were unaffected and all were CDe/c. In 1956, during her fifth pregnancy, antibodies were detected for the first time. The highest titer was 1:128. Spontaneous labor occurred at 41 weeks. The infant was severely affected. The cord hemoglobin was 5.4 grams per cent. Two exchange transfusions were performed; the infant survived and is normal. During her sixth pregnancy in 1963 the highest indirect Coombs titer was 1:256. Amniotic fluid was obtained at 34 and 35 weeks' gestation and the findings recorded in the manner described by Liley are shown in Figure 1. The values are in the middle zone indicating moderate hemolytic disease. In spite of the history of a previously severely affected infant the pregnancy was allowed to progress to 37 weeks' gestation. The infant survived with three exchange transfusions.

Case 2

A 35-year-old para 5-0-0-4 patient was blood group O, cde and her husband was blood group A, CDE/c. One parent of the husband was cde. The first two infants were Rh positive. The second was severely affected but survived with kernicterus. In 1959 a hydropic infant with a cord hemoglobin of 2.8 grams per cent was delivered after induction of labor at 36 weeks' gestation but did not survive. In 1961 labor was induced at 36 weeks and an Rh negative infant weighing 3590 grams was delivered. Another Rh negative infant was delivered in 1963. In 1965 the indirect Coombs titer was 1:1024 at 16 weeks and dropped to 1:256 at 32 weeks' gestation. Amniotic fluid was obtained at 34 and 38 weeks (Figure 2). Spectrophotometric analysis of the amniotic fluid showed lower zone values, and an Rh negative infant was delivered at term.

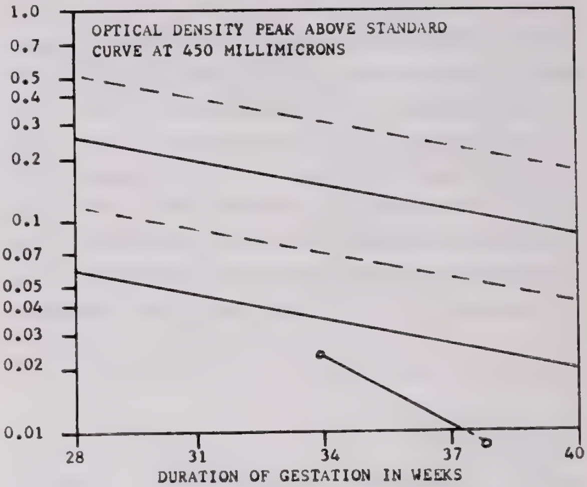

Fig. 2

Amniocentesis at 34 weeks and 38 weeks. Elective induction of labor by amniotomy at 39 weeks. Infant — female, 3580 grams, blood group O, cde, direct Coombs neg. Cord blood — HGB 18.8 gm%, bilirubin 2.2 mg%.

Summary

The obstetrical history, the Rh antibody titers, the prenatal course, and the Rh genotype of the husband provide only minimal information concerning the severity of the hemolytic disease of the fetus in utero.

Amniotic fluid analyses are of great value to identify Rh negative unaffected fetuses and to evaluate the severity of the hemolytic disease when present.

Preterm and premature delivery with immediate exchange transfusion can salvage a large proportion of infants who otherwise would be stillborn or liveborn with hydrops fetalis.

In a small number of selected patients, perhaps 5 to 8%, intrauterine fetal transfusion may be necessary to allow the fetus to achieve adequate maturity prior to delivery.

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6-21 May be secured from the author or the reprints.

Put off your imagination as you do your overcoat when you enter the laboratory lest it hinder your observing power . . . but before the experiment and between whiles, let your imagination wrap you round.

— Claude Bernard, French physiologist (1813-1878)

Chronic Obstructive Airway Disease

Improvement in Pulmonary Function after Vigorous Program

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ALTHOUGH PULMONARY function may be of prognostic value in chronic obstructive airway disease,[1] rarely is improvement—as evidenced by results of a battery of pulmonary function tests—seen after vigorous treatment. The follow-up response to treatment of patients with such a condition is so often discouraging that it seems worthwhile to present a case in which significant objective improvement in pulmonary function was demonstrated after one year of therapy.

Case Report

A 68-year-old man was seen at the Mayo Clinic on August 31, 1964, because of progressive dyspnea and chronic cough of six years' duration. Besides smoking two packs of cigarettes every day for 49 years, he had been in the upholstering business for 40 years where he was exposed to dust and to fumes from lacquers. He had a long history of asthma with upper respiratory infections during the winter that dated back to childhood. His chronic cough had been productive of 2 oz. of clear sputum every day for 28 years. In addition, cold air, dust, fumes, and chemicals caused bronchospasm.

On examination he had dyspnea of grade 3. Breath sounds were diminished in the bases, and there were inspiratory and expiratory wheezes. There was expiratory slowing of grade 4 and the diaphragm moved only 1 cm. bilaterally. Chest expansion was limited to 1.5 cm.

A chest roentgenogram was interpreted as showing emphysema. There was a normal flora on routine sputum culture.

Pulmonary function tests on August 25, 1964, (Table) showed severe obstructive airway disease. There was an increase in the residual volume and in the ratio of residual volume to total capacity. The maximal breathing capacity was decreased considerably, and the maximal midexpiratory flow was only 0.4 liter per second. The nitrogen-washout index was elevated to 6.7%. The patient was desaturated at rest and became more desaturated after only 1.3 minutes of exercise, which was all he could tolerate.

A program of treatment for emphysema was initiated. This program included the drinking of 10 to 12 glasses of water each day, breathing exercises, and instruction in a dust-free room. He was instructed in the use of a nebulizer (Isuprel 1:200, 10 drops with 10 drops of distilled water three times a day). One bronchodilator tablet three times a day, one hour after the nebulizer, was prescribed. He was instructed to use tetracycline, 250 mg. four times a day for five days, when upper respiratory infection was noted or when his sputum was discolored.

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The patient returned on August 18, 1965, for a recheck of the chronic obstructive airway disease. He had been feeling well and was active physically, walking six blocks a day. He did not cough excessively and was averaging only ½ oz. of clear sputum per day. He had had no bronchial infections during the preceding year. On this examination (one year after the initial one) his chest expansion had increased to 3.8 cm. (1½ inches); his diaphragm moved 2 cm. bilaterally and the expiratory slowing was grade 2. The chest roentgenogram was interpreted as normal.

At this time the patient's vital capacity and maximal breathing capacity had increased and the nitrogen-washout index had decreased. There was less expiratory slowing, as shown by the maximal midexpiratory flow before and after the nebulizer was used (Table). The patient now has a normal arterial oxygen saturation at rest and after five minutes of exercise.

Discussion

A correlation has been found between the severity of emphysema at autopsy and the premortem values of vital capacity, maximal voluntary ventilation, and maximal midexpiratory flow rates.[2] Sweet and associates,[3] in an earlier publication, described a correlation between the ratio of residual volume to total capacity (RV/TC) and the morphologic findings of emphysema at autopsy. Boushy and Coates[4] have found four parameters of pulmonary function related to prognosis (maximal voluntary ventilation, forced vital capacity, carbon dioxide tension, and oxygen saturation). Abnormal tensions of arterial blood gas have been postulated as being related to prognosis[5] and of value in determining the onset of cor pulmonale.[6] Other workers[7] have stated that abnormalities of blood gas reflect the severity of the illness primarily in acute

Pulmonary Function Data in Chronic Obstructive Airway Diseases
Before (August 1964) and After (August 1965) Treatment

Function	Estimated Normal	Values in Aug. 1964	Aug. 1965
Pulmonary volumes			
Vital capacity (expiratory), liters	4.5	1.97(2.14)*	2.80(3.29)*
Inspiratory vital capacity, liters	4.5	2.11	
Residual volume, liters	1.5	4.06	4.05
Total capacity, liters	6.0	6.16	6.85
RV/TC x 100, %	45.0	66.0	59.0
Functional residual capacity, liters	2.7	4.88	4.27
Expiratory reserve, liters	1.2	0.82	0.23
Maximal breathing capacity, L/min.	96	29(37.0)*	61(83)*
Maximal midexpiratory flow, L/sec.	2.0	0.4(0.4)*	0.7(1.0)*
Expiratory slowing, grade (1-4)	0	4.0(4.0)*	3.0(2.0)*
Nitrogen-washout index, % N_2	≦2.5	6.7	1.7
Arterial oxygen saturation (oximeter), %			
Resting (air)	95-98	87	94
Resting (oxygen)	100	100	100
Before excercise (air)	95-98	92	96
Exercise (air)	No fall	83 (1.3 min)	95 (5 min.)
Exercise (5.0 min. in oxygen)	100	100	
Ventilation (at sitting rest, breathing oxygen)			
Volume (liters) per minute		12.55	11.21
Respirations per minute		20.0	15.0
Average tidal volume, ml.		627	747

*Values after treatment with Isuprel given in parentheses.

exacerbations. Chronic hypercapnia* is common in patients with chronic obstructive airway disease. Although the degree of carbon dioxide retention[8] reflects the severity of the acute illness, it still may be of prognostic value when combined with the RV/TC ratio, maximal breathing capacity, maximal midexpiratory flow, nitrogen-washout index, and arterial oxygen saturation. A vital capacity, maximal breathing capacity, and maximal midexpiratory flow before and after nebulization give an excellent index of the response to therapy. The failure of a response at the beginning of treatment, however, does not obviate the benefit from bronchodilators, as is shown in this case. The patient should be retested after he has been on a treatment program for several months.

Summary

A vigorous approach to chronic obstructive airway disease can bring about improvement in the pulmonary function. Herein is reported a case of a 68-year-old man who experienced significant improvement subjectively and objectively after one year of treatment consisting of a high fluid intake and breathing exercises, medication with expectorants, nebulizers, bronchodilators and intermittent antibiotics.

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*See Test Your Word Score Page 1107.

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Faxen's Syndrome

This eponymic term has been used to designate certain aberrations of behavior and body movements. The syndrome is characterized by playful and manneristic behavior, iteration, retropulsion, rigidity, and turning about the longitudinal axis. Although these abnormal activities are more often associated with schizophrenia, they may also occur as a manifestation of an encephalopathic complex that results from severe, prolonged periods of alcoholism. If the symptoms of the Faxen syndrome are relatively mild, the patient may recover. More serious cases may progress to a stage of cerebral degeneration.

Durham, Robert H. — Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

Derivatively Speaking

Telangiectasis — from Greek *tele* (at a distance) plus *angeion* (vessel) plus *ektasis* (dilatation)

in diarrhea

LOMOTIL® Tablets Liquid

Each tablet and each 5 cc. of liquid contains:
diphenoxylate hydrochloride . . . . 2.5 mg.
(Warning: May be habit forming)
atropine sulfate . . . . 0.025 mg.

is a corker

Effectiveness: Lomotil possesses a unique degree of effectiveness in both acute and chronic diarrhea.

Convenience: Lomotil is supplied as small, easily carried, easily swallowed tablets and as a pleasant, fruit-flavored liquid.

Versatility: The therapeutic efficiency, safety and convenience of Lomotil may be used to advantage alone or as adjunctive therapy in diarrhea associated with:

- **Ulcerative colitis**
- **Acute infections**
- **Irritable bowel**
- **Regional enteritis**
- **Drug therapy**
- **Food Poisoning**
- **Functional hypermotility**
- **Malabsorption syndrome**
- **Ileostomy**
- **Gastroenteritis and colitis**

Dosage: For full therapeutic effect – Rx full therapeutic dosage. The recommended initial daily dosages, given in divided doses, until diarrhea is controlled, are:

Children:	3 to 6 months	– 3 mg. (½ tsp.* t.i.d.)
	6 to 12 months	– 4 mg. (½ tsp. q.i.d.)
	1 to 2 years	– 5 mg. (½ tsp. 5 times daily)
	2 to 5 years	– 6 mg. (1 tsp. t.i.d.)
	5 to 8 years	– 8 mg. (1 tsp. q.i.d.)
	8 to 12 years	–10 mg. (1 tsp. 5 times daily)
Adults:	20 mg. (2 tsp. 5 times daily or 2 tablets 4 times daily)	

*Based on 4 cc. per teaspoonful.

Maintenance dosage may be as low as one-fourth the therapeutic dose.

Precautions: Lomotil, brand of diphenoxylate hydrochloride with atropine sulfate, is a Federally exempt narcotic preparation of very low addictive potential. Recommended dosages should not be exceeded. Lomotil should be used with caution in patients with impaired liver function and in patients taking addicting drugs or barbiturates. The subtherapeutic amount of atropine is added to discourage deliberate overdosage.

Side Effects: Side effects are relatively uncommon but among those reported are gastrointestinal irritation, sedation, dizziness, cutaneous manifestations, restlessness, insomnia, numbness of extremities, headache, blurring of vision, swelling of the gums, euphoria, depression and general malaise.

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Editorials

When the Cervical Pap Smear is Positive

ELSEWHERE IN THIS issue* is a resumé of a forum on the positive Pap smear presented at the last clinical meeting of the Minnesota State Medical Association.

That differences of opinion exist is not surprising, since the procedures followed are relatively new. One author's opinion is expressed as follows: "Tissue must be procured from the entire circumference of the junctional zone. Instrumentation, even the taking of office biopsies, may destroy the histologic evidence of early lesions." Just two paragraphs later the opinion is given that multiple cervical biopsies taken in the office are mandatory after a positive smear test. This writer has used both approaches. In earlier practice, office biopsies of the cervix were routine after a confirmedly suspicious or a positive smear test, even though the cervix appeared normal. This practice was later discarded because the yield of invasive carcinoma was nil, and the presence of intraepithelial carcinoma in the punch biopsies did not obviate the need for later conization to rule out invasive carcinoma elsewhere in the portio or canal. Another advantage of the more immediate approach, that of hospitalization and conization, is to cut short the suspense factor in the anxious patient. The authors point out, however, that sufficient time should be taken to treat vaginal infections and repeat suspicious smears to avoid the consequences of false positives.

The article states that total hysterectomy and intracavitary radium therapy are both acceptable forms of treatment in the young patient with carcinoma in situ. Here again is a debatable field. No doubt exists, however, that the surgical approach has an overwhelming majority of proponents, especially for the young woman in whom childbearing is completed. The surgically treated patient has both the psychological benefit of having the lesion-bearing organ extirpated and the advantage of avoiding symptoms of irradiation castration.

Treating young women with an intravaginal cone with kilovoltage techniques plus surgical replacement of the ovaries laterally is a new and interesting concept. This does not seem necessary, however, for the young woman who is willing to appear at regular intervals for smear testing and pelvic examination after a conservative conization biopsy removal of the in-situ lesion. When residual carcinoma is suspected after conization biopsy one wonders what effect on fertility will result if a cancerocidal dose of radiation is applied to the cervix.

Melvin B. Sinykin, M.D.
Minneapolis, Minnesota

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*See Page 1181.

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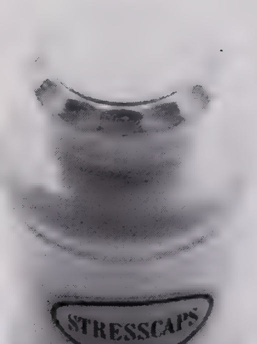

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The Bridge between Psyche and Soma

THE EXPRESSION of emotions by means of altered bodily functions is a daily observance. The blush of embarrassment; the pre-examination diarrhea; the muscle-contraction or tension headache, and many other "psychosomatic" phenomena are readily apparent. The more subtle expressions of emotions can show a myriad of variations. The practicing physician is often mystified by the import of the functional symptoms that tax his diagnostic acumen every day. We are all aware of the potential power of the common emotions of love, jealousy, resentment, anger, and rage. Throughout time these feelings have played a pivotal role in cultural, social, and individual development. Constant changes in the acceptable expression of these feelings through the evolution of a social, religious, and legal conscience has resulted in the development of inhibitory control patterns. These mechanisms, primarily acquired by observing and mimicking close family members, may take various forms. We are able to note the various mechanisms used by patients to avoid the anxiety of conflictual feelings. Repression, sublimation, rationalization, denial, reaction formation, introjection, projection, and displacement are words to describe the unconscious maneuvers used to prevent anxiety that would result if feelings were freely expressed.

Challman* has lucidly noted that the presence of hostility initiates these unconscious defense mechanisms. Anger is often turned inward or introjected** to produce the common psychoneurotic depressive reaction. The guilt attendant upon feelings of hostility seems to demand penance in the form of the long-suffering, self-depreciatory manifestations of depression. This condition, as well as the anxiety state noted when the mechanisms are insufficient to protect against the increasing flood of unacceptable emotions, is well known to physicians. Retreat from hostile impulses by regression, or projection of hostile impulses onto others in the form of paranoid ideas, may represent other ineffectual ways of handling overwhelming feelings of hostility. When these protective shields falter or fail, anxiety is the inevitable result.

Perhaps of greater concern to the diagnostician, however, are the somatic expressions of emotions. Hostility seems to be the most consistent feeling involved in psychosomatic conditions. When hostile impulses, which lie more or less dormant in all of us, threaten to emerge, anxiety results and the unpleasant feeling it produces is then channeled off in various ways. If the underlying hostility is not pervasive, and if a well developed set of defenses is present, the hostility may be expressed more or less overtly in a sociably acceptable manner, with relief of the tension generated. Sometimes the anxiety is expressed via various organ systems. The general bodily involvement with anxiety or rage is well known. Skeletal muscle tautness as a control over emotions is almost universal. The resultant muscle-contraction syndromes of tension headache, functional low back ache, and fatigue are probably the most common psychosomatic complaints. Certainly the old saw, "When you swallow resentment, you get indigestion," is an insightful observation. The effects of anger on the gastric mucosa have been known since Beaumont's observations. Likewise, many other organs and organ systems are influenced directly or indirectly by the emotional chain of events.

In order to maintain social order, hostility and its conscious expression, anger, have greater need to be under control than most feelings. The power inherent in hostile feelings, if measurable, would be an awesome quantity. The possibility that hostility is a basic force, such as sexuality or regressive trends, remains a moot question. Regardless of the answer, various conflictual feelings during the developmental years produce anger and hostility. Challman notes the long incubation period during which the hostile

Continued

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*Challman, Alan: Hostility and Disease. Minnesota Med 49: 523, 1966.

**See Test Your Word Score Page 1107.

"All Interns are Alike"

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impulses may be contained prior to the outbreak of symptoms. This delay may hinder the search for specific etiologic factors in the production of a functional or psychosomatic illness. It is only by a longitudinal survey of the patient's life with an emphasis on the methods he has used to control his feelings that a logical pattern of the psychodynamics productive of the physical symptoms can be explained and interpreted. It behooves all practicing physicians to be aware of the role that emotions play in producing and aggravating bodily symptoms. Without this understanding, meaningful therapy is difficult; with this knowledge, the bridge between the psyche and soma becomes a revealing link.

Maurice J. Martin, M.D.
Rochester, Minnesota

Planning Perfect Children*

MODERN FAMILY planning techniques make it possible for any married couple to plan the size of their family, the intervals between children, and the seasons of the year in which the children will be born.

However, simply to control the time of conception determines nothing about the outcome of the pregnancy except the probable time of delivery. After conception the parents wait and take their chances that the child they have conceived will be normal or abnormal; they must take their chances with recessive genes each carries which may be potentially handicapping or lethal. No knowledge exists that can alter this chromosomal roulette. The parents still take their chances with the factors of their nutrition, health, exposure to teratogenic agents** which can cause congenital malformations in a genetically "normal" child. Many of these agents and influences are known, as well as the likelihood that they will produce congenital abnormalities.

Ability to control conception and knowledge of many of the pre- and post-conception influences which can cause congenital malformations indicate that these influences are potentially controllable. For example, a woman who has not had rubella could, in the face of an epidemic, prevent conception until she had acquired and recovered from the disease. If similar control of the other environmental causes of congenital malformations is to be achieved, this knowledge must be made available to prospective parents through premarital and prepregnancy counselling.

This counselling would be prophylactic, aimed at preventing preventable malformations, to increase the likelihood that the child to be conceived will have a "perfect" body and mind. Prepregnancy counselling would also have to be comprehensive.

The key to success would be the teaching of adequate techniques for contraception control; modern techniques of contraception make prevention or control of conception simple. No couple need guess or wonder about how successfully they can avoid pregnancy; they can avoid it efficiently as long as they desire. When they wish to conceive a child they need only stop their contraceptive measures, and if they are normally fertile, conception is probable. The probability of conception can be abetted by tests which identify the time of ovulation and, therefore, the optimum time for conception.

The second step would be to establish optimum preconception health for the potential mother and father. The concern with their health prior to conception is more than an intuitive guess.

The father's spermatozoa begin to differentiate about 64 days before they are able to fertilize the ovum. The mother's ovum, formed in utero and arrested at prophase of the first miotic division, completes the first miotic division between the start of the menstrual cycle and ovulation. The second miotic division takes place after fertilization. Nongenetic alteration can occur in the chromosomes during this time. The process of miosis

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*USPHS Research Career Development Awardee K3-A1-14,035.
**See Test Your Word Score Page 1107.

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involves doubling of the chromosome number of the primary gonocyte. In the first miotic division the daughter cells each receive one half of the doubled chromosomes, and in the second miotic division one half of the normal cellular component. Abnormal division of the chromosomes in the sperm or ovum or abnormal crossover may cause doubling or loss of part of a chromosome. The frequency of abnormal miotic division or cross-over can be increased by some teratogenic agents, i.e., X rays, viral injections, and vitamin deficiencies. When such agents have been known to affect either parent during the period of miotic division of their germ cells, prudent parents would postpone pregnancy; on the other hand, when planning pregnancy, these parents would avoid such influences and maintain their health and nutrition at optimum levels.

When conception is desired the parents can plan for simultaneous ovulation and intercourse. Experimental evidence exists in almost all laboratory animals that the healthiest offspring are obtained when fertilization of this ovum is coincident with or close to ovulation. As the time interval increases, the incidence of malformations, stillbirths, and abortions increases rapidly.

The critical period following conception will require special emphasis. Guide lines will have to be laid down for the first weeks before pregnancy can be confirmed, for the remainder of the first three months, and for the remainder of the pregnancy. Organogenesis takes place during the first three months of pregnancy; during these months teratogenic agents can produce the more severe and readily apparent anomalies. Early in pregnancy the fetus is very susceptible; later it is much less susceptible to teratogenic agents. In the past, most teratogenic events have taken place before the mother knew for certain that she was pregnant or at least before she sought the care of a physician. With planned conception the mother will know when she is probably pregnant and within two or three weeks after conception that she is definitely pregnant. Knowing this, she can, if appropriately advised, take precautions to insure the optimum intra-uterine environment for her baby. The benefits to be gained are obvious.

Other factors which are related to malformations, such as age of parents, family size, recessive genetic disease in either kinship, would also be stressed. The responsibilities in rearing the child to attain his optimum potentials ought also to be discussed, for there would be little value in bringing a "perfect" child into existence if obvious environmental factors exist which might blight the growth of the child.

Society as well as parents ought to be concerned about this further application of medical knowledge. At present, congenital anomalies account for 25 to 40 per cent of stillbirths and 10 to 14 per cent of neonatal deaths. Such anomalies are present in 4 to 10 per cent of surviving infants and in severe forms in about 1 per cent; they account for over one third of the utilization of hospital beds during childhood. Although efforts directed at preventing congenital malformations should bring great and directly calculable benefits to society, they can be expected to bring far greater, although incalculable benefits, to families who have been spared the birth of a malformed child.

Enough facts are available to warrant clinical trials to prevent congenital malformations. Enough areas of ignorance exist to warrant extensive research into human teratogenesis.

Warren J. Warwick, M.D.*
Minneapolis, Minnesota

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*Department of Pediatrics, University of Minnesota Medical School.

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The Insurance Doctor's Slant on Hypertension

To EXPLAIN TO patients why they are charged an increased premium for their life insurance when their recent physical examination revealed a blood pressure which they were told need be of no concern to them, presents a touchy problem. For the physician who is expected to be as reassuring as possible, it is usually desirable to avoid alarming a patient when a blood pressure is borderline, because there is going to be an opportunity to re-examine him before any treatable problem arises. Because the life insurance medical department is involved in issuing a noncancellable lifetime contract, there is no opportunity for a re-evaluation to separate those who will eventually develop increased and definitely pathologic blood pressure from those who have transient random high readings. Therefore physicians in those departments must take a statistical approach toward blood pressures and for the most part use the Build and Blood Pressure Study, 1959, by the Society of Actuaries.

That study covered experience over the years 1935-1954 and excluded war-induced deaths. The fifth phase of the blood pressure was used for diastolic readings and the cases considered were only those which had no other serious impairments. A few significant examples show why problems arise. For example, in age 30-39, with a diastolic pressure of 68 to 82 mm. of mercury, systolic pressures of 138 to 147 will give an additional mortality of 30%, and 148 to 157 an additional mortality of 50% over the expected mortality for that age group. The expected mortality at age 30 in the U. S. total population based on the 1959-1961 data is 1.43 deaths per 1,000 per year.

To raise that by 30% or 50%, gives only 1.86 to 2.15 deaths per 1,000, a number hardly large enough to be noted in clinical practice. Again, at age 40-49, with diastolic pressures of 83-87 mm. of mercury, systolic pressures of 138-147 will give 55% extra mortality and 148-157 will give 130% increase in mortality. With the expected number of deaths of 3 per 1,000 for the U. S. population as a whole, even 4.6 to 6.9 deaths per thousand, the number dying each year, would be too small to be apparent clinically. If one goes further into the mortality tables, the blood pressures at which treatment is usually prescribed are associated with very high mortality rates, using the concept of the increase in deaths per thousand at any given year of age.

There have been no good statistical studies made as yet of insurance applicants who have been under extensive or extended antihypertensive therapy. Experimentally, insurance has been offered them. In discussing insurability with a patient, the physician should keep in mind that the insurance medical department is dealing with individuals on the statistical basis of the number of deaths per 1,000, whereas in most clinical problems, evaluations are made on the percentage of good results or survivors in a given group over a variable period of years.

John T. Smiley, M.D.
Minneapolis, Minnesota

Renal Arteriovenous Fistula*

IN A RECENT issue of MINNESOTA MEDICINE*, Naffah and co-workers have called attention once more to the occurrence of arteriovenous communications affecting the renal vasculature. Increasing evidence of the role of renovascular lesions in the pathogenesis of hypertension and the resulting more careful examination of the abdomen for the detection of abdominal bruits have uncovered numerous cases of this type. Recently we were able to collect from the world literature[1] reports of 68 cases of renal arteriovenous fistula in association with ipsilateral functioning kidney.

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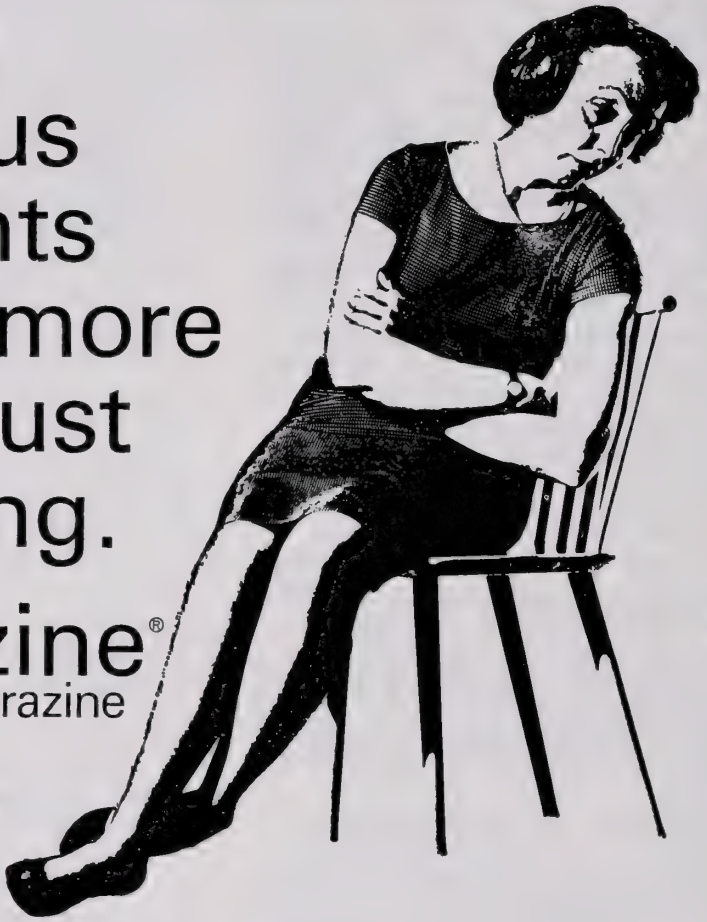
*Minnesota Med 49:227, 1966.

Many anxious patients need more than just calming.



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The causes of fistula included hypernephroma, inflammation, atherosclerosis, and trauma of different types: penetrating injuries, nonpenetrating injuries, nephrolithotomy, partial nephrectomy, and percutaneous renal biopsy. Finally there was a significant group of congenital and idiopathic origin.

A unique association of high-output cardiac failure, diastolic hypertension, and intra-abdominal bruit constituted a syndrome seen in about one third of the patients with fistula of the renal vessels.[1-3] The cardiac failure and bruit result from large fistulas in any location, but in the renovascular location perfusion of the ipsilateral kidney is reduced and hypertension occurs at the same time.

Asymptomatic fistulas have been detected in increasing numbers in recent years, mainly by means of aorticorenal arteriography. Many of these patients had had previous percutaneous renal biopsy. Bennett and Wiener[4] have recently emphasized the relatively frequent occurrence of renal arteriovenous fistula following renal biopsy. A most discriminative selection of patients for renal biopsy and reexamination of the patients, after biopsy, by means of abdominal and flank auscultation and perhaps by angiography may be indicated to detect renal arteriovenous fistulas following biopsy. Fortunately, in most of the cases associated with biopsy, the vascular lesion has been small and in general without clinical consequence. In some cases, healing has been observed after a few months.[4]

The importance of making a diagnosis of renal arteriovenous fistula is clear, since correction or removal of the fistula brings cure of the congestive failure, amelioration or cure of the hypertension and, in some cases, detection of an underlying malignant tumor presenting with cardiovascular manifestations only.

The ideal form of treatment of renal arteriovenous fistula is demonstrated in the case reported by Naffah and colleagues. The authors repaired the vascular defect and saved the kidney in spite of very difficult circumstances. This constitutes indeed a highly commendable achievement, since in most reported cases the kidney was removed. Whenever possible, the fistula should be repaired.

Jorge E. Maldonado, M.D.
Sheldon G. Sheps, M.D.
Rochester, Minnesota

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Meningococci Resistant to Chemotherapy*

IT HAS BEEN known since the early days of microbiology that microbes have great capacities in vitro to adapt to noxious agents, provided that the stimulus is applied in graduated degrees over long periods. Thus, disinfectants in small concentrations lead to the development of forms resistant to doses which would be lethal to the original strain of the organism. This is why the continuous use of chemotherapeutic agents such as sulfonamides and antibiotics inevitably leads to the development of some forms of the infecting organism resistant to the drug in question. Multiplication of the drug-resistant forms leads to the predominance of these mutants over the sensitive forms, which soon cease to exist in a person receiving sulfonamides. There is no real evidence that the

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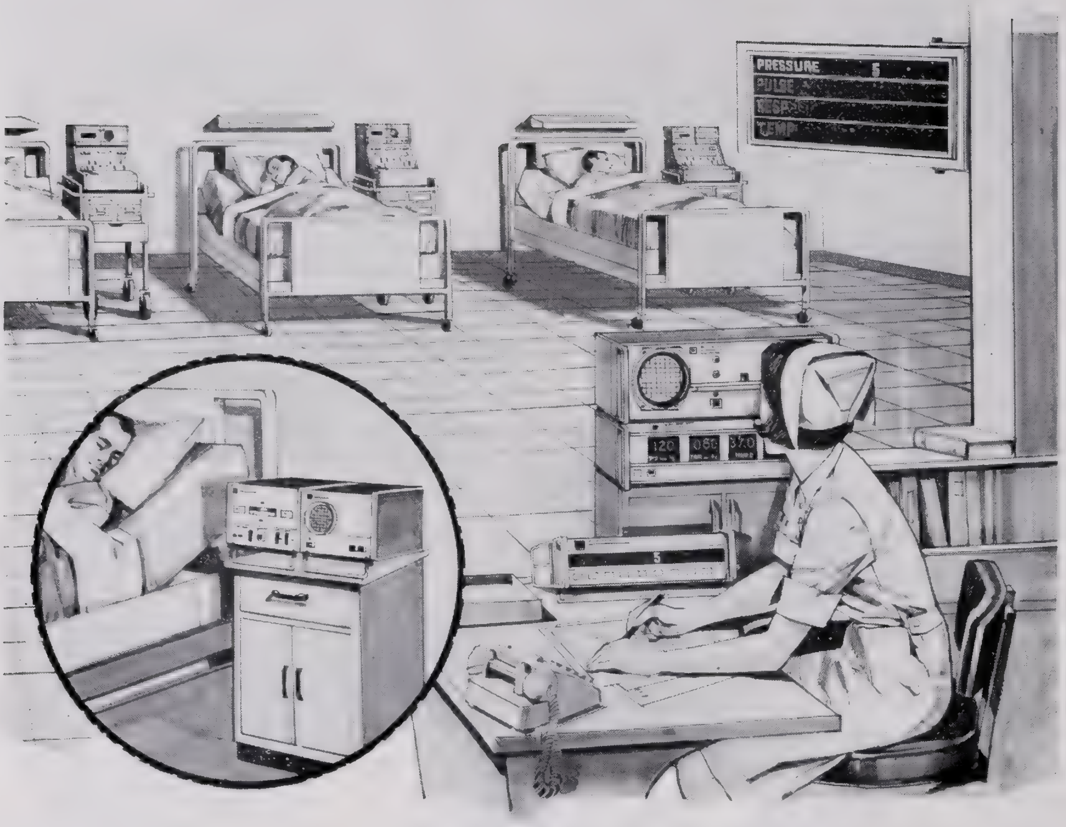
*Walker, A., and Strom, R. L.: Sulfonamide-Resistant Neisseria Meningitidis in Minneapolis. Minnesota Med 49:232, 1966.



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drug-resistant forms are any less capable of producing disease than are the original organisms, and they do make treatment more difficult. This problem is very nicely presented in the study, "Epidemiology of Meningococcal Meningitis at Fort Ord,"[1] by Gauld, Nitz, Hunter, Rust, and Gauld. These workers found that, because of the generally increased resistance of the organisms concerned, the prophylactic use of sulfonamides was of little or no value in the prevention of infection. Since sulfonamides possess real hazards, it is doubtful if they should be used except therapeutically against known infection. It is important to recognize that there are sulfonamide-resistant forms among the various serologic types of meningococci, and that a suitable method for determination of the susceptibility of these forms to the drug is available. However, when infection caused by meningococci is at hand, time may not always permit such tests and the empiric use of drugs may be necessary.

Although serologic typing is an important epidemiologic tool, there is no proof that it is of prognostic value or that what it discloses is related in any way to the factor of virulence.

Lyle A. Weed, M.D.
Rochester, Minnesota

Reference

1. Gauld, J. R., Nitz, R. E., Hunter, D. H., Rust, J. H., and Gauld, R. L.: Epidemiology of Meningococcal Meningitis at Fort Ord. Amer J Epidemiol 82:56, 1965.

Test Your Word Score

Erythema infectiosum — *mild infectious disease resembling measles* (page 1057).

Poltophagy — *chewing food fine; from Greek poltos (porridge) plus phagein (to eat)* (page 1060).

Psomophagy — *swallowing food in pieces; from Greek psomos (morsel) plus phagein (to eat)* (page 1060).

Protean — *variable, changeable* (page 1061).

Aerobic — *living in air* (page 1078).

Logarithmic — *if the fixed number is 10 the logarithm of 1000 is 3* (page 1082).

Perinatal — *before, during or after delivery* (page 1083).

Hypercapnia — *an increased* CO_2 *tension resulting in extra stimulation of the respiratory center* (page 1091).

Introjected — *appropriation of external happening making it a part of one's self* (page 1097).

Teratogenic agent — *a substance causing a disturbed growth process involved in the production of a monster* (page 1099).

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— Adlai Stevenson

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Geigy

The Editor's Soliloquy

Advice to the Graduates

For the past few years you have been given progressively increasing responsibility; now you have graduated and are going into practice. Whether on your own or as a partner you will continue to have others with whom you must be reasonably compatible.

The first requisite for a viable and successful relationship is mutual respect. Unless you have the highest esteem for the men in the medical profession, do not consider partnership. However, if you do decide to affiliate with someone, do so on the basis of a flexible agreement for a year or two; it will keep you from cumbersome, binding contracts, until you can be certain that personalities do not clash. Moreover, when you do prepare a contract, make it simple and basic; a contract should be designed to keep the heirs from destroying the survivor, should one of you die.

Your associate will be somewhat older than you; defer to his seniority. Do not underestimate his intelligence; it is as good as yours. Consult with him; ask his advice — discuss your medical problems man to man without personalities. You may have some revolutionary ideas; his may be more conservative, having been established by experience and vindicated by time. Learn to say: "You may be right."

Don't quibble over minutiae; stick to fundamentals. Never drive home a point or clinch an argument. You may be the winner — but you lose anyway!

Do not count your cases or try to match your workload with your partner's; for then you are impugning his integrity and giving him cause to doubt yours. Work at your natural pace; carry your full share and, if possible, a bit more for good margin.

Do the work of a doctor, not that of an assistant. Consign to nurses, secretaries, and accountants the work of nurses, secretaries, and accountants. Be gracious and kind to your subordinates but never familiar.

As for your patients: make their welfare the paramount consideration in your career. It was for service to them that you entered the medical profession and took the Hippocratic oath. Let no shadow of venality tarnish your image. Keep a damper on your tongue; it was designed to be a persuasive and versatile organ, not a rapier. In short, be impeccable in your manners toward all with whom you come in contact. There is no substitute for good breeding.

Accept your full share of civic responsibility within and without the medical profession, but unless you are aiming to make it a career, stay out of politics.

Educate your children but remember that there is more than one good school. The public one supported by your taxes has produced many distinguished men. Furthermore, the majority of successful men in the world received the most valuable part of their education from their fathers and mothers.

Uphold the dignity of your profession without pomposity or condescension.

Mom says: The only place that success precedes work is in the dictionary. — C. O. R.

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1. Schleif, R.H.: J.A.PH.A., 46:179,1957 *U.S. Pat. No. 3,062,714

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Our Senior Educators

Jennings Crawford Litzenberg, M.D.

Born April 6, 1870 — Died August 15, 1948, of a Coronary Occlusion

"Your name is already on the roll of honor of those who have contributed to the development of a great University." This tribute from President Lotus B. Coffman to Dr. Litzenberg at the time of his retirement expresses the esteem of those who knew him as a teacher and a scholar. He was truly the "Giant of the North" in the fields of obstetrics and gynecology. His contributions locally and nationally earned for him the respect, admiration and gratitude of colleagues, students and patients. In every sense of the word he was a rare person and a true gentleman.

Dr. Litzenberg's background was a fascinating one. Born in the village of Waubeek, Iowa, he was a fifth-generation American on both paternal and maternal sides. His ancestry was a mixture of German, Scotch-Irish, English and Welsh. Both of his great-great grandfathers fought in the Colonial Army in the American Revolution. When he was six years old, the

Continued

family moved to a larger town, Anamosa, where his father practiced law. In his autobiography he recalls how he and his widowed mother "blew" into Minneapolis in March of 1890, where he registered the next fall at the University of Minnesota with the intention of studying law. However, it was not long before he changed to a scientific course as preparation for the study of medicine.

There were obstacles during this period. Trouble with his eyes and insufficient funds delayed his education. There was an interim of one year which he spent as Superintendent of Schools in St. Louis Park; but immediately thereafter posts as Educational Director of Evening Schools at the Minneapolis Y.M.C.A., and employment by Dr. L. J. Cooke, Physical Director at the University of Minnesota, enabled him to enter the Medical School, from which he graduated in 1899. A year's internship in the Minneapolis General Hospital served as a foundation for general practice in Medicine. During the next two years he had an office where, to use his own words, he "practiced more economy than medicine."

On June 3, 1902, he married Elizabeth Fisher of the Class of 1898, who bore him two children, Avis and Karl, Professor of English at the University of Michigan since 1929. "Liz" and "Litz," as they were affectionately known, enjoyed a happy marriage. For his ideals she willingly sacrificed the added comforts that a greater continuity of practice could have brought, and in return he eagerly embraced her ideals in the spiritual realm of church, music and the home.

In 1927, when Dr. Litzenberg had reached the height of his career, Elizabeth Litzenberg died. Seven years later he married Dr. Olga Hansen, a member of the Department of Medicine at the Nicollet Clinic. This union was also blessed. As each followed his or her career in medicine, there was compatibility of interests and a mutual sharing of their love and esteem with the families and friends of each.

From 1901 until 1907 Dr. Litzenberg served first as Instructor in Obstetrics at the University, then as Assistant Professor. He received no compensation except "valuable experience and a great interest in the subject." In 1909 he departed with his family for Vienna, where for two years he studied under the great Dr. Schauta. A reorganization of the Medical Faculty in 1913 resulted in his appointment as Professor and Chief of the Department of Obstetrics and Gynecology, in which capacity he served for twenty-five years, until he reached the retirement age of 68. Almost immediately following this appointment, he returned to Europe for additional study in Vienna, Berlin, Glasgow and Dublin.

During Dr. Litzenberg's incumbency, his department in the Medical School did not require full time, and he continued private practice, first with a small staff of associates in his specialty. In 1921 he joined a group of men to form the Nicollet Clinic for group practice. From this association he retired December 31, 1947, because of ill health. He was widely employed as a consultant.

At the time Dr. Litzenberg ascended to the chair of Obstetrics and Gynecology, teaching was entirely for the benefit of the undergraduates. There were no residents. Internships were not a necessary requirement for the degree of M.D. until as late as 1920. Graduate study was undertaken almost entirely in Europe, especially in Germany. Soon after its reorganization in 1913, the Medical School of Minnesota developed and adopted a system of Teaching Fellowships in order that graduate study in the various fields of medicine and surgery would be available. Graduate students were required to take didactic courses; to perform supervised clinical work; to participate in teaching, and, finally, to present a research thesis, the satisfactory completion of which led to the conferment of a Ph.D degree. About a dozen men received their training in obstetrics and gynecology under Dr. Litzenberg while he occupied the chair. The influence of these men was considerable.

Dr. Litzenberg was one of the most sought-after medical speakers in this area. In addition to his speaking, practice and teaching, he completed during the years a number of important research projects. To mention only a few: he was the first to study the relationship between hypothyroidism and fertility; he made classical contributions to the understanding of tubal pregnancy; he interested himself in the problem of tuberculosis during pregnancy in his capacity of obstetrical consultant to the Glen Lake Sanitorium; and he studied the leukocytes in pregnancy. His bibliography, while not as extensive as that of some of his contemporaries, is distinguished by a style that is meditative, conservative, precise, forceful, and on occasions, clairvoyant. His last major work was "The Synopsis of Obstetrics," C. V. Mosby and Co., published in 1940 and re-edited in 1943.

The reduction in the maternal mortality rate may be the best evidence of Dr. Litzenberg's influence in this community. At the time he accepted the chair of Obstetrics and Gynecology, the maternal mortality rate in Minnesota, although one of the lowest in the country, was almost 7 per 1000 births. In 1920 about 15,000 women died in the nation as a consequence of child-bearing. By 1930 a marked diminution of the maternal mortality rate was noted, not only in Minnesota, but in adjacent states. That the influence of his powerful teaching was largely responsible for the decline is unquestionable; it is estimated that by 1930 about one half of the practitioners in this area had been his students. By 1947 Minnesota had a record of 0.6 maternal deaths per 1000 live births, the lowest ever recorded in this country, if not in the world.

From the beginning, Dr. Litzenberg's creative approach to the problems in his field drew national attention. In 1915 he was made a member of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, an organization that he served as president in 1933-34. In 1916 he was elected a Fellow of the American Gynecological Society. Twenty-five years later he was elected to the presidency. In the preceding year the Central Association of Obstetricians and Gynecologists honored him with the office of president. In 1927 he served as the chairman of the Section of Obstetrics and Gynecology in the American Medical Association.

In 1920 he was chosen as a member of a small committee of obstetricians and gynecologists to consider the establishment of an American Board of Obstetrics and Gynecology. This was prompted by a growing agitation in the medical profession, as a whole, for some method to identify the trained specialist, because the increase in the number of pseudo-specialists in multiple fields had become alarming. In 1930, after ten years of careful study and investigation, this committee established the American Board of Obstetrics and Gynecology, one of the first examining boards to come into existence. Dr. Litzenberg was elected to the board of nine as one of the

Continued

three members from the American Gynecological Society, a post he retained until his resignation in 1940.

He served locally as president of the Hennepin County Medical Society in 1918, the Minnesota Academy of Medicine in 1932, and the Minnesota Obstetrical and Gynecological Society in 1937. "I have prized these honors," he said, "because they came from my home societies where the members knew my faults."

It has been said of Dr. Litzenberg that he illustrated in striking degree the dictum so often voiced by the late Dr. James E. Moore. "The true conservative is one who knows when to be radical." This is probably a brief summation of "Litz's" philosophy of the practice of medicine. He was a pioneer in his field and a personification of the meaning of his own name — "A Light in the Mountains."

Ray F. Cochrane, M.D.
Minneapolis, Minnesota

Note: Material condensed from An Appreciation given by Dr. S. Marx White before the Minnesota Academy of Medicine, An Appreciation by Dr. Claude J. Ehrenberg which appeared in MINNESOTA MEDICINE in December, 1948, and an Autobiography written by Dr. Litzenberg at the time of the 50th Reunion of the Class of 1894.

It Must be Good for Something!

Overweening faith in drugs is supposed to be a characteristic particularly of ignorant, unthinking people who are readily suggestible. I remember in the early days of my practice feeling that I was in the presence of a typical example of this ignorant feeling toward drugs when a good old colored woman who used to do cleaning for us consulted me one day. She had in her hand a large bottle of medicine which the lady of the neighboring house had asked her to throw out, telling her, by the way, that though it had cost two dollars it had never been used. The old colored woman did not like to think that this much money should be wasted, especially when it was a question of "real medicine prescribed by a doctor." So she brought the bottle to me to ask me if I could possibly find anything the matter with her for which the medicine might do good. . . . I had often heard of eating things in order not to have to throw them away, but this was my first experience with saving medicines that way. Alas, I could find nothing the matter with her. So the medicine had to go, but not without a deal of poignant regret on Aunt Sally's part. Later when I heard the story of how Carlyle, hearing that his friend Henry Taylor was ill rushed off to see him with what was left of some medicine which had helped Mrs. Carlyle, — the English philosopher thinking that it would surely do his friend good, too, though he did not know what had been the matter with Mrs. Carlyle nor what was now the cause of Taylor's illness, I knew that my experience with the colored woman was just the result of a human failing for the mysterious ways of medicine and not at all due to ignorance. Just think for a moment all that Mrs. Carlyle might have had the matter with her which Taylor, from the very nature of things could not possibly have had the matter with him. Yet here was one of the deepest thinkers of the nineteenth century hurrying to him with his wife's medicine, confident it must do him good as it had her.

— James J. Walsh, M.D., Ph.D., Sc.D.: Cures, 1924.

Curbstone Consultation

Contraceptive Pills

QUESTION: A patient taking contraceptive pills has reported swelling and discomfort in the legs which disappears when she discontinues the medication. Are there other sequelae associated with this type of medication? Is it attributable to the contraceptive pills?

Answer: Numerous side reactions to the oral contraceptive pills have been reported. Most of these have been mild and consist mainly of those which might be attributed to water retention — mainly weight gain, swelling of the ankles, bloating of the abdomen, and occasionally nausea. Breakthrough vaginal bleeding and spotting have been troublesome for some patients.

More serious reactions such as papilledema, severe headaches, blurred vision or vertigo have occasionally been reported. A few patients have been noted to present an elevation of blood pressure. These patients and those with a history of cerebral vascular accidents should be advised not to take the pills. There has been some question as to whether there was an association between these tablets and thromboembolic disease, but this has never been definitely established. Patients with a history of malignancy of the breast or reproductive system, nursing mothers, patients with a history of thromboembolic phenomena, and emotionally disturbed patients should not use these tablets. Patients who take the newer oral sequential contraceptive tablets have reported fewer of these disturbing side effects.

Mancel T. Mitchell, M.D.
Clinical Associate Professor,
Obstetrics and Gynecology
Minneapolis, Minnesota

Mosquito Control

QUESTION: Are there any nontoxic drugs which can be used for mosquito control?

ANSWER: Paracelsus said "Dosis sola facit venenum" (The dose makes the poison). There are no non-toxic drugs. The materials presently used for mosquito control can be used without harm if used properly, but even the least toxic materials can cause injury if used improperly.

Mitchell R. Zavon, M.D.
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Indications: Meprobamate is effective in relief of anxiety and tension states. Also as adjunctive therapy when anxiety may be a causative or otherwise disturbing factor. Although not a hypnotic, meprobamate fosters normal sleep through both its anti-anxiety and muscle-relaxant properties.

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Precautions: Careful supervision of dose and amounts prescribed is advised. Consider possibility of dependence, particularly in patients with history of drug or alcohol addiction; withdraw gradually after use for weeks or months at excessive dosage. Abrupt withdrawal may precipitate recurrence of pre-existing symptoms, or withdrawal reactions including, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, the dose should be reduced and operation of motor vehicles or machinery or other activity requiring alertness should be avoided if these symptoms are present. Effects of excessive alcohol may possibly be increased by meprobamate. Grand mal seizures may be precipitated in persons suffering from both grand and petit mal. Prescribe cautiously and in small quantities to patients with suicidal tendencies.

Side effects: Drowsiness may occur and, rarely, ataxia, usually controlled by decreasing the dose. Allergic or idiosyncratic reactions are rare, generally developing after one to four doses. Mild reactions are characterized by an urticarial or erythematous, maculopapular rash. Acute nonthrombocytopenic purpura with peripheral edema and fever, transient leukopenia, and a single case of fatal bullous dermatitis after administration of meprobamate and prednisolone have been reported. More severe and very rare cases of hypersensitivity may produce fever, chills, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, anaphylaxis, stomatitis and proctitis. Treatment should be symptomatic in such cases, and the drug should not be reinstituted. Isolated cases of agranulocytosis, thrombocytopenic purpura, and a single fatal instance of aplastic anemia have been reported, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity has been reported, usually after excessive meprobamate dosage. Suicidal attempts may produce lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

Usual adult dosage: One or two 400 mg. tablets three times daily. Doses above 2400 mg. daily are not recommended.

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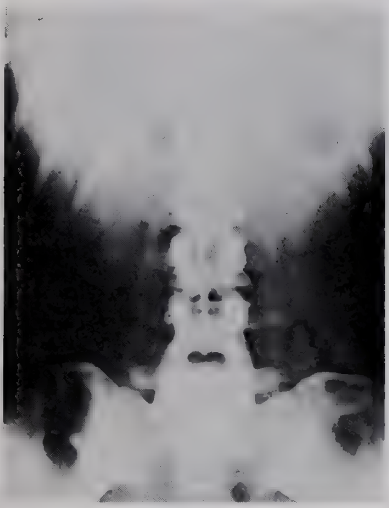

Figure 1

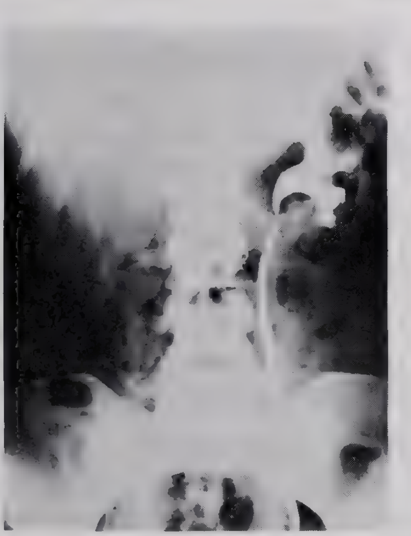

Figure 2

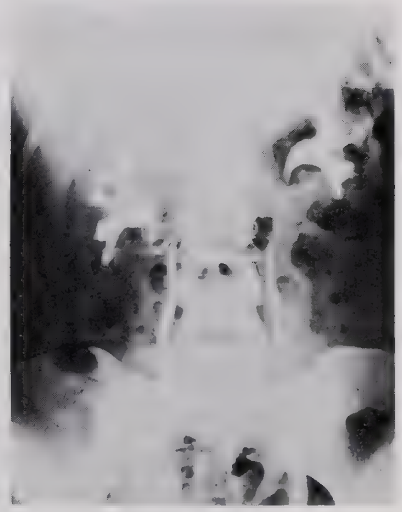

Figure 3

A 29-year-old woman was first admitted to St. Barnabas Hospital in August 1965 for right renal colic. The only previous illness was an episode of pelvic inflammatory disease three years before after her last delivery. She had had no previous renal disease. Physical examination was unremarkable except for right flank and right lower quadrant tenderness. Laboratory work-up revealed 15-20 RBCs on a catheterized urine specimen and a white blood count of 17,000. BUN. and fasting blood sugar were normal. Calcium and phosphorous determinations were also within normal limits. The K.U.B. film revealed several calculi over the right renal shadow. A non-compression urogram showed poor excretion on the right with eventual filling on delayed films. There was evidence of hydronephrosis with caliectasis and a stone lodged in the distal right ureter. At cystoscopy the following day a 4-mm. stone was removed from the bladder. The patient was subsequently discharged.

In October 1965 the patient was readmitted with left renal colic. Roentgenographic examination showed no function in the left kidney even on delayed films. The stones in the right kidney appeared to have increased in size (Figure 1). Bilateral retrograde pyelograms showed characteristic findings of renal papillary necrosis (Figures 2 and 3). A stone was passed spontaneously and sent to the laboratory for examination. Pathologically this was a necrotic papilla.

From the preceding story one can fairly readily make a roentgenographic and pathologic diagnosis of renal papillary necrosis. However, one pertinent piece of information was not mentioned regarding the patient's history.

What is your diagnosis? (See next page)

DIAGNOSIS: Renal Papillary Necrosis due to Phenacetin Toxicity.

The patient claimed that three years ago she developed headaches. Since that time she consumed 10-12 APC tablets daily but discontinued taking the pills after the diagnosis of papillary necrosis was made.

Phenacetin has been a common ingredient in cold tablets and proprietary headache mixtures for years. In 1953, Spuhler and Zollinger[1] were the first to incriminate phenacetin as a causative agent in renal papillary necrosis. Larsen and Moller[2] in 1959 reported their experience at the Municipal Hospital at Zerjle, Denmark. Their inquiry among 698 patients revealed that 205 (29.4%) took phenacetin-containing drugs daily. Renal function in these patients was found to be reduced in 33% of the cases. The incidence of reduced renal function was increased with higher dosages and duration of administration. The authors concluded that a patient who has taken 1 grain of phenacetin (5-7 pills) daily for ten years has an 80% chance of reduced renal function.

Recently reports have been appearing in the American literature.[3-5]

There are several distinctive almost pathognomonic, roentgenographic findings in renal papillary necrosis: (1) There is a small cavity formation connected to the calyx at one central point. This finding is observed only when the central and apical portion of the pyramid is involved.[5] (2) The ring shadow sign may be seen early in the disease. This may appear first as a small curvilinear line or streak of contrast material starting from the edge of the calyx. Eventually the line will form a complete ring, which represents the sloughed edge of the necrotic papilla. This sequestered portion will either fragment, disintegrate, or pass out of the ureter with or without symptoms of ureteral colic. It may calcify within the cavity it forms. (3) A large triangular cavity that forms after sloughing of the papilla is an almost pathognomic sign of renal papillary necrosis.[5] Usually each calyx has only one cavity, but occasionally composite calyces contain two or even three pyramids. (4) The calcification of the necrotic portions of the papillae assumes fairly characteristic forms. The x-rays show triangular or rounded rings of calcification with a radiolucent center.[5]

Differential Diagnosis

One must consider such entities as pyelorenal backflow, calyceal diverticula, pyelogenic cysts, sponge kidneys, neoplasms, blood clots, pyelonephritis, tuberculous and renal calculi. However, if one keeps in mind the characteristic roentgenographic findings of renal papillary necrosis and the history of diabetes[6] or especially excessive phenacetin intake, the diagnosis of this entity should not be too difficult.

Frank E. Mork, Jr., M.D.*
Minneapolis, Minnesota

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*Department of Radiology, St. Barnabas Hospital.

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1. Spuhler, O., and Zollinger, H. U.: Die Chronisch-interstitielle Nephritis. Z Klin Med 151:1, 1953.
2. Larsen, K., and Moller, C. E.: Renal Lesion Caused by Abuse of Phenacetin. Acta Med Scand 165:321, 1959.
3. Moolten, S. E., and Smith, I. B.: Fatal Nephritis in Chronic Phenacetin Poisoning. Amer J Med 28:127, 1960.

4-6 May be secured from the author or the reprints.

Fracture–Trauma Conference

Dislocation of the Metacarpophalangeal Joint of the Index Finger

Dislocation of the index finger metacarpophalangeal joint is a rare finding in spite of the frequent trauma that the entire hand is subjected to. It differs from the more common dislocation of the other fingers such as the thumb and the small finger in that it almost always requires an open reduction to reduce the dislocation.

In 1957 Kaplan described in detail the anatomic pathology in such a dislocation. He found that fibrocartilaginous plate breaks away from the volar aspect of the second metacarpal and becomes displaced inside the metacarpophalangeal joint. The metacarpal head is wedged between the two groups of transverse fibers in the palmar fascia and fibrocartilaginous plate, while the long flexor is displaced to the ulnar side.

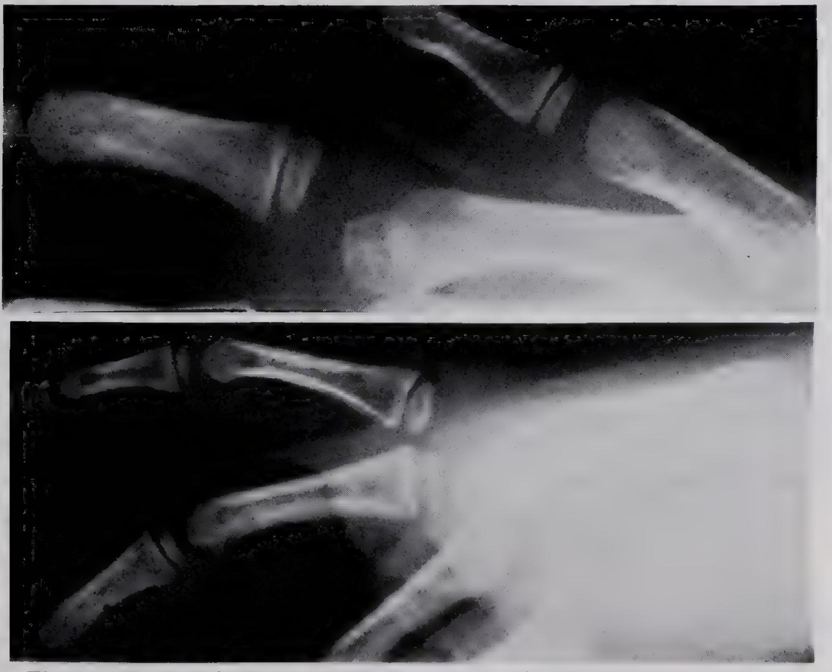


Fig. 1-a (top), 1-b (bottom) — Anteroposterior and lateral projection showing dislocation of the metacarpophalangeal joint of the index finger.

Continued

This case is presented for two reasons: first, because metacarpophalangeal dislocation almost always requires an open reduction; second, because it is a rare entity.

Case Report

A five-year-old boy sustained an injury on May 10, 1965, when a cement block fell on his hand. An x-ray taken by the family physician showed a dislocation of the metacarpophalangeal joint of the index finger. Closed reduction was done several times under local anesthesia. All of the reduction attempts ended in failure. The finger was splinted and the child sent to us for orthopedic consultation.

On examination of the index finger it was found to be swollen, particularly at the metacarpophalangeal joint. The joint was deformed in hyperextension and very tender to pressure or passive motion. The neurovascular status was normal.

The roentgenogram of the hand showed a metacarpophalangeal dislocation characterized by volar displacement of the metacarpal head with a relative ulnar and dorsal displacement of the proximal phalanx (Figures 1-a and 1-b).

Under general anesthesia two attempts at closed reduction were made but were unsuccessful. An anterolateral incision was then made at the metacarpophalangeal joint, retracting the neurovascular status dorsally and the flexor tendon ulnarwards. As expected, there was a large defect in the volar capsule where the metacarpal had button-holed through it. The volar fibrocartilaginous plate was interposed between the metacarpal head and the proximal phalanx, and the metacarpal attachment was found detached (Figure 2). With the volar plate in its displaced position open reduction was tried, but this too was unsuccessful due to the blocking effect of the volar plate. After the volar capsule opening was enlarged and the volar plate pushed anteriorly, the metacarpal head was snapped back to its normal position, articulating with the base of the proximal phalanx. Attempts to redislocate the metacarpophalangeal joint demonstrated that the reduction was stable. The capsule was sutured with two interrupted sutures and the skin closed with continuous 6-0 wire and placed on a volar splint in a functional position for 10 days. In three to four weeks the motion progressed to a near normal state. The patient was seen again six months after surgery. The finger was normal in all aspects.

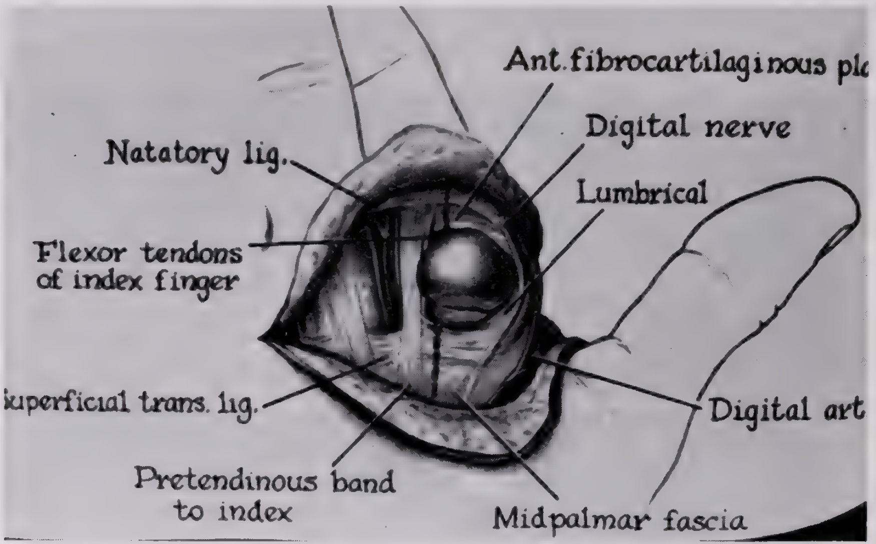


Fig. 2 — Anatomical derangement in metacarpophalangeal joint dislocation of the index finger as illustrated by Kaplan. (Reproduced with permission from the editor of the Journal of Bone and Joint Surgery.)

Discussion

Our case confirms Kaplan's findings of a displaced volar plate and torn volar capsule. The displaced volar plate is mainly responsible for the failure of closed reduction. As soon as it is placed in its normal position the dislocation is easily reduced and appears to be stable without any tendency to redislocation. It is also conceivable that the dislocation may be reduced from the dorsum, if the fibrocartilaginous plate can be displaced volarwards. If this is not feasible, the recommended approach will be volar, to effect a successful reduction.

Ramon B. Gustilo, M.D.
Minneapolis, Minnesota

Requests for reprints should be addressed to the St. Louis Park Medical Center, 4959 Excelsior Blvd., Minneapolis, Minnesota.

Reference

1. Kaplan, E. B.: Dorsal Dislocation of the Metacarpophalangeal Joint of the Index Finger. J Bone Joint Surg 39-A:1081, 1957.

The Minnesota State Board of Medical Examiners

Notice is hereby given, pursuant to the provisions of Minnesota Statutes, 1965, Section 15.0412, that the Minnesota State Board of Medical Examiners will hold a public hearing on Saturday, July 16, 1966, at 10:00 o'clock a.m. in the Colonial Room of the Lowry Hotel, Saint Paul, Minnesota, on the adoption of the following proposed changes in the Rules and Regulations of the Minnesota State Board of Medical Examiners:

1. The adoption of a new Rule and Regulation ME 7 (a) (8) reading as follows:

"(8) On all applications filed on or after July 1, 1968, evidence satisfactory to the Board that the applicant has been awarded a Standard Certificate by the Educational Council for Foreign Medical Graduates, certifying to the applicant's formal education, his having passed the ECFMG English test, and his having passed the American Medical Qualification Examination of the ECFMG."

The effect of the proposed New Rule and Regulation ME 7(a) (8) is that from and after July 1, 1968, graduates of foreign medical schools who apply for admission to a licensing examination must furnish evidence satisfactory to Minnesota State Board of Medical Examiners that the applicant has been awarded a Standard Certificate of The Educational Council for Foreign Medical Graduates, in addition to the other information required by ME 7 (a).

2. The amendment of Rule and Regulation ME 6 by striking and deleting therefrom ME 6 (b) (6) and by substituting in lieu and in place thereof:

"(6) Evidence satisfactory to the Board that the applicant has been awarded a Standard Certificate by The Educational Council for Foreign Medical Graduates, certifying to the applicant's formal education, his having passed the ECFMG English Test, and his having passed the American Medical Qualification Examination of the ECFMG."

The effect of the proposed amendment to Rule and Regulation ME 6 is to conform to present practice by eliminating the requirement by applicants for a temporary certificate for graduate traning, that they be registered by Minnesota State Board of Examiners in the Basic Sciences, and by substituting the requirement that they have been awarded a Standard Certificate of The Educational Council for Foreign Medical Graduates, in addition to the other information required by ME 6 (b).

Interested persons are invited to attend and submit data or views orally or in writing.

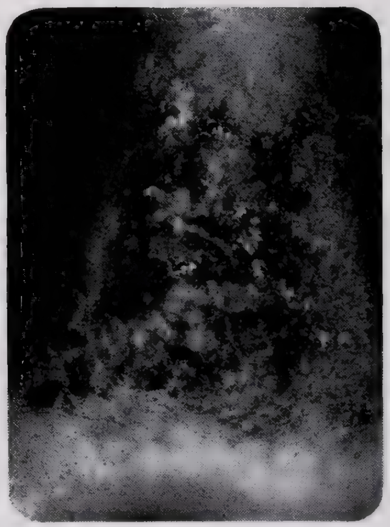
Dated at Saint Paul, Minnesota, this 13th day of May, 1966.

J. P. Medelman, M.D.
Secretary-Treasurer

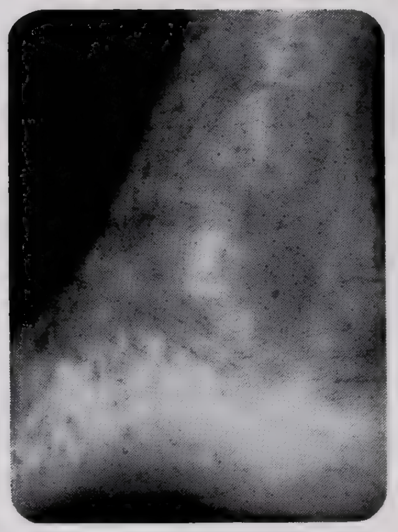
Talk

Wise men talk because they have something to say; fools, because they have to say something. — Plato

eczema: scourge of childhood



R. R., Age 11—Before treatment—
atopic eczema of long standing



After treatment—with ARISTOCORT
Topical Ointment 0.1% for two weeks

ARISTOCORT® Triamcinolone Acetonide Topicals have proved exceptionally effective in the control of various forms of childhood eczema: allergic, atopic, nummular, psoriatic, and mycotic.

In most cases responsive to topical ARISTOCORT, the 0.1% concentration is sufficiently potent. The 0.5% concentration provides enhanced topical activity for patients requiring additional potency for proper relief.

Administration and Dosage: Apply sparingly to the affected area 3 or 4 times daily. Some cases of psoriasis may be more effectively treated if the 0.1% Cream or Ointment is applied under an occlusive dressing.

Contraindications: Tuberculosis of the skin, herpes simplex, chicken pox and vaccinia.

Precautions and Side Effects: Do not use in the eyes or in the ear (if drum is perforated). A few individuals react unfavorably under certain conditions. If side effects are encountered, the drug should be discontinued and appropriate measures taken. Use on infected areas should be attended with caution and observation, bearing in mind the potential spreading of infection and the advisability of discontinuing therapy and/or initiating antibacterial measures. Generalized dermatological conditions may require systemic corticosteroid therapy. Steroid therapy, although responsible for remissions of dermatoses, especially of allergic origin cannot be expected to prevent recurrence. The use over extensive body areas, with or without occlusive nonpermeable dressings, may result in systemic absorption. Appropriate precautions should be taken. When occlusive nonpermeable dressings are used, miliaria, folliculitis and pyodermas will sometimes develop. Localized atrophy and striae have been reported with the use of steroids by the occlusive technique. When occlusive nonpermeable dressings are used, the physician should be aware of the hazards of suffocation and flammability. The safety of use on pregnant patients has not been firmly established. Thus, do not use in large amounts or for long periods of time on pregnant patients.

Packages: Tubes of 5 Gm. and 15 Gm.; ½ lb. jar.

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618-6

Neuro-Pediatrics Conference

Agammaglobulinemia, Meningitis and Mental Retardation*

THIS TEN-YEAR-OLD boy, originally referred for evaluation of possible immune deficiency, was more recently referred for evaluation and assessment of his developmental potential in school.

Dr. Robert Christensen:**

The past history reveals that pregnancy, labor and delivery were uneventful with normal growth and development up to five years of age. At five years of age he developed pneumococcal meningitis, complicated by severe seizure activity, prolonged coma, and a two-to-three-week period of blindness in the recovery state. Neuromotor performance recovery was slow and intellectual function remained impaired. At age 8½, he was considered to be functioning intellectually at approximately the five-year level.

For the last two years he has been in a speech class at Winnetka School, where his participation has been characterized by a reasonable degree of social maturity but a notable lack of progress in acquiring basic reading and writing skills. His physical growth and development have been within normal limits since the meningitis.

Seizure activity was encountered for a year or so after the meningitis; however, this has been well controlled by medication (Mebroin and Peganone) since that time until ten months ago, when he had one grand-mal seizure during a stay in the University Hospital. Because of recurrent infections and a family history of agammaglobulinemia he was hospitalized, and a diagnosis of agammaglobulinemia of the Bruton type was made. Since that time he has received 20 cc. of gammaglobulin intramuscularly at 28-day intervals and has been relatively free of clinical evidence of infection.

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*Held on Wednesday, September 15, 1965 at 1 p.m. in Hibbing, Minnesota.

Sponsored by the U. S. Public Health Service Grant N2502A63. These conferences are an integral part of the Comprehensive Clinic Program at the University of Minnesota Hospitals. The pediatric conferences are held weekly from 1 to 2 p.m. every Wednesday. The adult conferences are held every Thursday at 4 p.m. Co-ordinators for the project are Dr. Edward C. Defoe and Dr. Charles Branthaver in Pediatrics and Dr. Robert Soll in Adult Neurology.

**Student physician, University of Minnesota Hospitals.

Continued

Dr. Edward Defoe:*

Mrs. Moon, you were really the instigator of this referral for developmental evaluation. Will you give us a summary of your observations.

Mrs. Helen Moon:**

This boy's problems were detected when he was in kindergarten and special classes were recommended. I received him in my class two years ago. This is a class of 15 to 20 developmentally retarded students in the educable range. At this time at age eight, although his vocabulary was not that of the normal eight-year-old, he appeared in some ways quite advanced in relation to the other youngsters who were below normal in their I.Q. He was not overly distractable or easily upset emotionally. I never observed any type of seizure. However, his progress was much slower than that of the other children. He had great difficulties in discrimination and was unable to pick out specific objects in a group. In this first class most learning is based upon development of vocabulary and of ideas. At the end of the first year everyone in this group except Mark had accomplished enough to proceed to the next level for the educable group. We started over with him this last year. For the first few weeks he was not well, but as he recovered he once again became interested in pre-reading academic skills.

We had an opportunity to compare his performance with a trainable group, and although he was not gaining academically, he still seemed socially and otherwise more intelligent than the trainable group. However, at the end of the second year, it was difficult to come up with any positive gains.

Dr. Defoe:

Can you be more specific with regard to how he is more socially aware?

Mrs. Moon:

Well, he has very few physical manifestations of retardation as compared to the usual trainable child. He is able to look after himself very well as far as physical care is concerned; his table manners are good, and he seems cognizant of what is going on. He is aware of the duties involved in police regulation, school rules and postal service. These community helpers (as we call them) the trainable child would not recognize. In other words, I think he conducts himself in many ways like any normal little boy. Currently he is with the youngest educable group. This eight-to-nine-year-age group is beyond him academically, however.

Dr. Phillip Spieth:†

The two Stanford-Binet tests in 1963, about six months apart, revealed developmental quotients of 42 and 46, figures I believe to be reliable. The Bender test done last year was quite remarkable in that there was no correspondence between the pictures drawn and those presented. He showed some skill with pencil lines which were steady and straight; however, he was unable to duplicate the simplest pictures.

Dr. Michael Blaw:‡

On neurological examination this boy showed little if any neurological deficits other than those of higher function. No paralysis or spasticity was noted. He had some difficulty with coordinate movements and was clumsy with rapid alternating hand movements, which may well indicate some involvement of the cerebellum. Within the context of a classical neurological examination, there was no impairment of his peripheral visual system. I was impressed with his social abilities and the rather marked discrepancy between social abilities and academic performance. In general, there was good evidence for diffuse brain involvement. Pneumococcus is one of the more malignant organisms causing residual symptoms from meningitis because it has a tendency to produce lesions deep in the sulci of the cortex. Seizure activity, electroencephalographic abnormality with an active left temporal and frontal spike focus and over-all slowing, and his developmental status strongly suggest diffuse involvement with superimposed areas of more localized abnormalities. His future will be determined more by the diffuse than by any focal involvement.

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*Department of Pediatrics, University of Minnesota and Conference Moderator.

**Former teacher, Robbinsdale School District #281.

†Psychologist, Robbinsdale School District #281.

‡Pediatric neurologist, University of Minnesota Hospitals.

Dr. Defoe:

Dr. Blaw, does the time of onset and type of insult influence progress? Would you be more optimistic about this boy's future than about one with similar developmental retardation secondary to a congenital developmental defect?

Dr. Blaw:

I think it is reasonable to conclude that any residual of his meningitis at the present time is fixed and no further recovery can be expected. This does not mean he may not acquire more skills as he grows; but at this point it is not practical to predict whether this child will be able ultimately to function independently.

Dr. Richard Hong:*

This is a tragic case of irreversible central nervous system disease secondary to severe pneumococcal meningitis. We know that agammaglobulinemic children are particularly susceptible to severe bacterial infection and may have repeated bouts of meningitis.

Prevention

One of the important questions which we as physicians must always ask is "Could we have prevented or minimized this situation?" Inasmuch as one form of agammaglobulinemia is inherited as a sex-linked recessive disease, the history of frequent childhood infections when considered in the light of the history of death in two of the male siblings could very well have been the red flag we needed. Early administration of gamma globulin diminishes the incidence of the recurring extracellular pyogenic infections to which these patients are prone. However, pneumococcal meningitis causes severe complications as a result of the very viscous exudate it provokes, so that once the infection had occurred in this case, I believe the outcome was unrelated to the basic disease.

Clinical Characteristics

The clinical characteristics exhibited by patients with the Bruton

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*Pediatrician, University of Minnesota Hospitals.

Continued

type of agammaglobulinemia include: (1) recurrent severe bacterial infections caused primarily by pyogenic organisms; (2) poorly developed lymphoid tissue; (3) extremely low concentration of gamma globulin in the blood and tissue; (4) frequent hematologic abnormalities including frequent episodes of granulocytopenia and occasional lymphopenia; (5) a high frequency of rheumatic and collagen disease; (6) a high frequency of chronic pulmonary disease leading to bronchiectasis, and (7) an inordinate susceptibility to malignant lymphoid disease.

Diagnosis

The diagnosis is not difficult to make. But the use of paper electrophoresis is not accurate enough in the low ranges for reliable quantitation. Too many children have been labeled as hypogammaglobulinemics and treated with repeated gamma globulin injections for a condition which was in truth no more than a physiological variation. There is also some danger associated with prolonged gamma globulin administration. We have seen a number of serious anaphylactic reactions to gamma globulin in our patients.

Although the definitive diagnosis of hypogammaglobulinemia depends upon immunological tests which are not generally available in most clinical laboratories, there are many very informative procedures which, if positive, lead to a presumptive diagnosis of hypogammaglobulinemia. These include:

1. Zinc turbidity zero or insignificant.
2. Positive Schick test even after diphtheria toxoid.
3. Total protein low with a high albumin-globulin ratio even in the presence of chronic infection.
4. Minimal tonsillar and adenoid tissue by lateral nasopharyngeal x-ray.
5. In patients of blood group A, B, or O, isoagglutinins against heterologous blood group absent.
6. Bone marrow or lymph node biopsy showing no plasma cells even after antigenic stimulation.
7. Capillary precipitation test with rabbit antigamma globulin antiserum negative.

In the technical sense the term agammaglobulinemia is incorrect, as immunochemical determinations reveal the presence of significant gamma globulin in each patient. It is interesting that affected individuals, although very susceptible to bacterial infection, show a surprising capacity to resist virus infection.

Treatment

The treatment for agammaglobulinemia is replacement therapy with gamma globulin in much the same way as insulin is given for diabetes. Unfortunately, parenteral gamma-globulin administration is not the complete answer to the problem. Although it does aid in the prevention of such bacterial infections as meningitis, otitis media, etc., these children develop progressively severe chronic pulmonary disease and eventually die from it. The pulmonary diseases may be due to the lack of another immunoglobulin (gamma A) which we believe is of importance in prevention of infection of mucosal surfaces. The gamma-globulin preparations we have available at this time do not provide gamma A in amounts or in forms which can be secreted onto the mucosal surfaces.

Dr. Defoe:

I assume then that even though this boy appears to be free of pulmonary disease at the present, his potential life span is limited.

Dr. Hong:

Yes, I believe that is true. Not only are these children susceptible to chronic pulmonary disease; they are also more prone to develop malignancy than the random population.

Miss Helen Kretchmer:*

The parents appear to be a rather understanding family living in an average community with a very good school. The father is in the trucking business, and the mother is a secretary in an administrative office in the school. Their income is reasonable. Of the five children, the two girls have been healthy and well adjusted. Unusual is the fact that all the boys in the family have had tragic illnesses. One boy expired ten years ago with polio, and the second boy died last year with pneumonia. The lives of these boys were apparently full of illness.

The mother is conversant with medical terminology not just on a superficial basis but in a very discerning way. I think it is possible to make the same mistake with her that we might with medical personnel in assuming that she understands her own emotional reactions to the problems and not give her the support she needs for continuing to withstand the emotional buffeting she will receive. She has had considerable support from physicians caring for her children. However, she states she would like to have one doctor to whom she could go for advice and ongoing support.

The entire family helps in the patient's care, although the father is somewhat more impatient than the rest. They took the child to Yellowstone Park this year and said he was a delightful traveler. He learns by experience, likes to talk and see things. He tends to his own personal care and has never been a problem with conduct. He does try such activities as roller skating, tricycle riding, throwing a ball, and he is reasonably careful in the water. His mother is greatly concerned regarding what the future will hold; she would very much like direction.

Dr. Harold Ireton:**

Recent University of Minnesota Hospitals testing was supplemented by evaluation of social maturity (Vineland) plus screening for reading achievement, visual discrimination and visual motor coordination.

The total psychological evaluation indicates a child who is generally retarded in his mental functioning, operating in the lower end of the educable retarded range (WISC Verbal I.Q. 53). The Vineland Scale indicates general social maturity at about the 5½-year-old level. Generally, in intellectual and social functioning, Mark is operating at a five-to-six-year-old level. There is no particular evidence of outstanding abilities or marked deficiencies. Screening for visual discrimination (matching geometric forms) indicates simple perceptual discrimination consistent with

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*Social worker, University of Minnesota Hospitals.

**Certified Clinical Psychologist, University of Minnesota.

Continued

the above mental-age level. However, in a test of visual-motor coordination (copying geometric forms), he is operating significantly below the five-year-old level.

On a test of reading (Jastak) he demonstrated Reading Grade 1.1., which places him at mental age six. He is able to read some letters but no words. On the arithmetic subtest of the WISC, he achieved no success. He demonstrates rote counting but was unable to apply this to a concrete series of blocks. However, this did not seem to represent a perceptual problem, but rather a problem of comprehension and conceptualization. For example, when the examiner said "Count these. . .one. . .two, etc." he picked up the examiner's count at "two", pointed to the first block and continued in order from "two".

This child's school learning problems appear primarily associated with his generally limited mental ability and concreteness plus the fact of his difficulty in performing complex tasks requiring coordination or integration, whether mental or motor. Such problems in mental and motor coordination are consistent with his neurologic history.

Mrs. Judy Edmonds:*

The most obvious difficulties he had were with the tests concerning his conception of the relationship of one thing to another. He does not have good right-left orientation; nor does he appear to have a good bottom-top orientation. Considerable difficulty was encountered with manipulations guided by vision. He didn't understand the concept of difference but did grasp the concept of alike. For instance, I could give him one large cardboard alphabet letter and he could pick out one like it in a group on the table. If he was asked to find one that was different, this was always beyond him. He is a sensitive child and appears to be reacting strongly to the many failures he must have encountered. He does a good deal of verbal bluffing. He has some verbal skills and used them for purposes of distrac-

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*Speech pathologist, University of Minnesota.

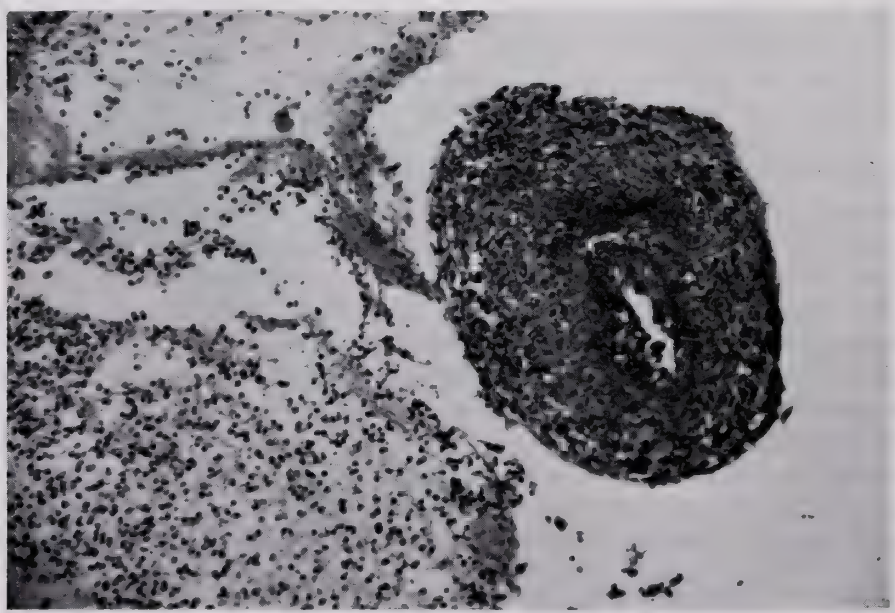

Fig. 1 — Arteritis — pneumococcal meningitis

tion. It was my feeling in view of his general developmental retardation, lack of spatial orientation, poor motor coordination and deficiencies in basic background for reading that perhaps now is not the time to try to teach him to read. Rather than concentrating on reading, development of basic concepts of right and left, up and down, and help in the use of these in a discriminating way will be more profitable. He needs help with spatial relationships and form constancy (always seeing a circle for a circle no matter how large or small); he also needs help in eye-hand coordination and many other similar skills. All of these will have to be developed at a gross level involving his whole body: from movements dealing with large objects down to figures and forms on a blackboard, and finally to something on paper.

Mrs. Moon:

This is essentially what we have done in class with almost no progress.

Dr. Frank Lassman:*

What I consider significant in this case is that the child does better in visual tests when motor requirements are not involved. We have observed this fact so often as to give constancy to our data. I tried to teach him letters and sounds yesterday by simple repetition reinforcement, and he responded very nicely. I feel that we will perhaps go farthest with this approach; however, how far he will be able to go remains to be determined.

Dr. Defoe:

There are several problems here. The point has been made that in his current group he performs well socially but is unable to learn and compete academically. However, placement in a class for trainable children might well hamper his social development.

In summary, this is a ten-year-old boy with agammaglobulinemia (Bruton type) who evidences general intellectual retardation secondary to

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*Audiologist, University of Minnesota Hospitals.

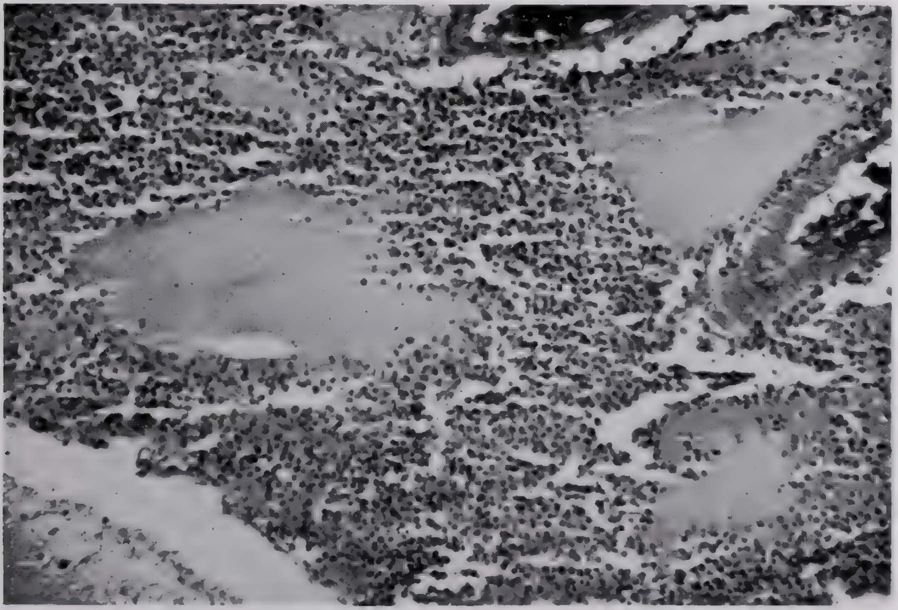

Fig. 2 — Purulent exudative myelitis

Continued

pneumococcal meningitis occurring at five years of age. Although in the last two school years he demonstrated progressive social developmental gain, he has shown no progress in the acquisition of basic spatial concepts necessary for the development of academic skills such as reading and writing. Enrollment in a class for educable retarded children will be continued throughout this year for promotion of his social education, with tutorial supplementation by Mrs. Peterson, directed toward acquisition of basic spatial concepts. Decision as to his ultimate school placement will rest upon evidence of progress attained during this coming year.

The boy's mother has expressed a need to have one physician for continuity of ongoing advice and support. Although Drs. Defoe, Ireton and Christensen will be responsible for interpretation of this conference to the parents, responsibility for ongoing support should be returned to Dr. Green (referring physician). The University can continue to offer aid in the management of the agammaglobulinemia to the extent that Dr. Green feels this is necessary.

Addendum

Damage to the cerebral cortex in these cases results mainly from hypoxia (these patients are particularly liable to aspiration, shock and impaired ventilation), vascular occlusion (thrombosis of small cortical veins — Figure 1) and bacterial encephalopathy (necrosis is especially prominent adjacent to regions of heavy subarachnoid exudate — Figure 2).

The neurologic sequelae of meningitis due to the three principal pathogens (D. pneumoniae, H. influenzae, N. meningitidis) run as high as 20% in surviving patients. The incidence of sequelae also runs high in the infant group, with the neonatal group the highest.

In a study of mentally retarded children in whom the defect was attributable to disease after birth 14 of 129 cases followed meningitis.

Edward C. Defoe, M.D.
Conference Moderator

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2. Swarz, M. N., and Dodge, P. R.: Bacterial Meningitis — A Review of Selected Aspects. New Engl J Med 272:725, 779, 842, 898, 954, 1003, 1965.

Participating in Conference

Mrs. Phyllis Amacher, Psychologist, Robbinsdale School District #281; Mrs. Helen Moon, former teacher, Robbinsdale School District #281; Dr. Spieth, Psychologist Robbinsdale School District #281; Mrs. Audrey Kuhnley, teacher, Robbinsdale School District #281; Mrs. Patricia Peterson, tutor, Robbinsdale School District #281; Mrs. Judy Edmonds, Speech Pathologist, University of Minnesota; Dr. Edward Defoe, Pediatrician, University of Minnesota; Dr. Michael Blaw, Pediatric Neurologist, University of Minnesota; Dr. Harold Ireton, Psychologist, University of Minnesota, Dr. Robert Christensen, Student Physician, University of Minnesota; Dr. Richard Hong, Pediatrician, University of Minnesota, and Dr. Frank Lassman, Audiologist, University of Minnesota.

Drive Safely

The motorist with any regard for his future abode should sing hymns as the speedometer climbs upward, a minister said in a safety sermon. These are his selections for the various speeds:

At 55 miles: "I'm Nearing the Port and Will Soon be at Home"
At 65 miles: "When the Roll is Called Up Yonder, I'll be There"
At 75 miles: "Lord, I'm Coming Home"

The Protestant Voice

Treatment of Peptic Ulcer

Presented as a Seminar
Sponsored by
The Faculty of the Mayo Graduate School of Medicine

THE MAGNITUDE of the peptic ulcer problem can best be described by the fact that 10% of all adult males in the United States will have this disease at one time or another in their lives. In order to approach the treatment of peptic ulcer rationally, it is necessary, first, to consider the pathogenesis; but the bulk of this paper will then be directed toward management of duodenal ulcer, to be followed by short discussions of postoperative recurrent ulcer, the Zollinger-Ellison syndrome, and gastric ulcer.

Pathogenesis of Peptic Ulcer

In examining the available information on the cause of peptic ulcer, one fact stands out above all others: mucosal ulceration occurs only in areas bathed by acid. The universal healing of peptic ulcers when there is achlorhydria also serves to establish gastric acid as a potent aggressive factor in ulcer formation. The importance of gastric acid in the pathogenesis of this disease is modified by the fact that not all ulcer patients are hypersecretors; as many as half of duodenal ulcer patients have normal outputs of gastric acid. Therefore, it appears that, in addition to the aggressive potential of hydrochloric acid, a breakdown in defense mechanisms is a significant factor in this disease.[1]

Gastric Acid Secretion

Cephalic Phase. — The cephalic phase was demonstrated by Pavlov by "sham feeding" dogs. He noted that this phase of gastric secretion was blocked by vagotomy. This vagal mechanism seems to be of great importance in duodenal ulcer patients who have high nocturnal and basal acid secretions. This pattern of hypersecretion is stopped by vagotomy. In addition to direct stimulation of gastric secretion of hydrochloric acid, the vagus has been shown to stimulate liberation of the hormone of the antrum of the stomach (gastrin) when this area is bathed in alkaline juice. A second portion of the cephalic phase has been postulated by Shay[2] who noted that hypersecretion in stressed persons was delayed three to four hours after an unpleasant incident. He attributed this response to activation of the hypothalamus-pituitary-adrenal axis. However, increased steroid levels have not been demonstrated in ulcer patients.

Antral Phase — Food in the stomach stimulates gastric secretion in the absence of a cephalic phase. Dragstedt[3] proved the pyloric antrum to be an endocrine organ which secretes the hormone gastrin, and this substance stimulates the parietal cells to secrete acid. The stimulus to the antrum is the chemical nature of food or the distention of the antrum by food in an alkaline medium. An acidic pH in this region will effectively reduce gastric secretion, thus serving as a regulatory mechanism at the completion of gastric digestion. Some investigators think that an inhibitory hormone is also secreted by the antrum for regulation of parietal cell function. Another inhibitory hormonal mechanism for control of gastric secretion is thought to be centered in the duodenum. Dragstedt[3] suggested that the antral mechanism is the most logical expla-

Continued

nation for the development of benign gastric ulcer. This condition is characterized by normal to low secretion of gastric acid. He postulated that the ulcer diathesis is created by obstruction to the passage of food into the duodenum, either mechanical or motor, thus causing constant antral stimulation. As support for this he cited the high incidence of gastric ulcer after vagotomy without drainage procedures and the 20% coincidence of duodenal ulcer with gastric ulcer. However, others think that this might be explained better by decreased resistance of the gastric mucosa.

Intestinal Phase. — The intestinal phase of gastric secretion has been demonstrated in animals in which the cephalic and antral mechanisms have been bypassed, but its place in the pathogenesis of peptic ulcer is not evident.

Maximal Output. — There is a good correlation between the total parietal cell mass and the maximal output of acid in response to histamine. The averages of both of these parameters tend to be high in groups of patients with duodenal ulcer and low-normal in those with gastric ulcer, but there is a large overlap with normal values in patients with duodenal ulcer.

Other Factors

Numerous mechanisms involving the pancreas have been implicated in peptic ulcer disease. These include hormone release in pancreatitis, hypoglycemic vagal stimulation, and decreased neutralization by alkaline pancreatic secretions. A hormonal mechanism similar to that in the Zollinger-Ellison syndrome has not been demonstrated in the pathogenesis of ordinary peptic ulcer.

Defense Mechanism. — Since the aggressive factors have not provided a complete explanation of peptic ulcerogenesis, defects in defense mechanisms must be considered. The local defense consists of three barriers. The first of these is the gastric mucus which forms a protective coating for the more susceptible, underlying mucosa. Certain drugs and, perhaps, disease states are thought to affect the integrity of the gastric mucus. Secondly, the regenerative capacity of the mucosal cells provides quick replacement of cells lost because of a breach in the mucous coating. Finally, the basic cellular resistance to digestion is much greater in the stomach and duodenum than it is lower down in the digestive tract. This is the so-called gradient of resistance. Other postulated defects in mucosal defense include local ischemia, allergy, and infection. There is no doubt that nutrition plays an important role.

Heredity. — The hereditary aspects of this problem can be shown by the preponderance of blood type O in duodenal ulcer patients and the lack of secretion of ABO factors in the saliva by many of these patients.

Drugs. — The effects of drugs in the pathogenesis of peptic ulcer can be described in several categories:[4] (1) local trauma (aspirin, phenylbutazone) ; (2) changes in mucus (steroids, aspirin) ; (3) stimulants of acid secretion (reserpine, caffeine) ; and (4) decreased regeneration (steroids, 5-fluorouracil.

Personality. — The significance of the "ulcer personality" in the pathogenesis of peptic ulcer is a much debated subject. A consensus seems to be that ulcer patients have no more anxiety than do other persons in the same positions in life. They are, perhaps, more inwardly directed, but this is not firmly established. Many experienced physicians think that there is no distinct ulcer personality.

Medical Treatment of Duodenal Ulcer

The treatment of duodenal ulcer is open to controversy on almost all points because of the natural history of spontaneous remissions and the lack of large, controlled studies on the various facets of management.[5,6] This allows opinions to vary from the concept that duodenal ulcer runs its own course regardless of therapy to the concept that every effort should be made to obtain a physiologic gastric environment, and includes the psychiatrically oriented idea that administration of antacids and anticholinergics is merely a subtle form of psychotherapy. Most clinicians think that maintenance of a bland gastric milieu promotes ulcer healing, but they argue about the relative merits of the various therapeutic measures.

Diet

Small feedings of bland foods are utilized in the treatment of acute ulcers to promote stomach rest by decreasing gastric motility and avoiding gastric stimulation by distention. Because of their tendency to increase acid output, dietary proteins are restricted early in the course of treatment. The classic regimen of milk alternating with an antacid every half hour has been liberalized by some to three bland meals and interim snacks for the initial treatment of duodenal ulcer.

Rest

Physical rest is an important part of the treatment, and some physicians consider this alone as the major factor in healing. Adequate sedation may be necessary to allow the patient to obtain adequate rest. Most duodenal ulcer patients need not be hospitalized, but this chance for complete rest should not be denied high-risk patients or those with unfavorable home situations.

Antacids

Neutralization of the stomach contents to a pH greater than 4.5 has been shown to inactivate pepsin. Antacids are known to be removed rapidly from the stomach and, in order to be effective, should be given hourly. The ideal antacid is cheap, does not cause systemic acid-base problems or rebound secretion, and is palatable. The insoluble antacids (aluminum hydroxide and magnesium trisilicate) have approached this ideal and have reduced the threat of hypercalcemia.

Anticholinergics

The dual action of anticholinergic drugs in decreasing secretion of hydrochloric acid and decreasing gastric motility would appear to make them ideal therapeutic agents. Although these agents have been shown to decrease basal acid output, their most significant effect appears to be relief of pain by alleviation of spasm. A warning has been issued that relief of pain without promotion of healing may lead to laxity in other therapeutic measures and thus to less adequate long-term control. The masking of tachycardia in early bleeding by use of anticholinergics has been noted as a dangerous characteristic. However, the consensus seems to be that anticholinergics are of value in the treatment of peptic ulcer, especially when acid output is high. This whole issue is subject to debate, however, because of lack of controlled studies.

Avoidance of Stimulants and Gastric Irritants

Probably the least controversial phase of the management of duodenal ulcer is the need for these patients to avoid gastric stimulants, such as alcohol and caffeine, ulcerogenic drugs, and environmental stress. The role of smoking in ulcerogenesis is less well established. However, the retarding effect of cough on ulcer healing and the 20% incidence of ulcer in patients with chronic pulmonary disease suggest that ulcer patients should not smoke.

Recurrence

Recurrence of duodenal ulcer is an integral part of the natural history of this disease. It has been stated that 50% of duodenal ulcer patients will experience a recurrence within two years. Prevention of this phase may be summarized as follows:[7] (1) patient's acceptance of control rather than cure of his disease; (2) continual avoidance of stimulants and irritants with no return to a normal diet; (3) elimination of stress when possible and special vigilance in times of unavoidable stress; and (4) patient's acceptance that recurrent symptoms are serious.

Complications

The complications of duodenal ulcer include obstruction, perforation, hemorrhage, and intractability. When these occur, certain criteria for choosing medical or surgical treatment are helpful.[5]

Obstruction. — Obstruction secondary to duodenal ulcer requires hospitalization, strict medical therapy, avoidance of anticholinergic drugs, and stomach aspiration

Continued

twice daily (morning and evening). After seven to 10 days, retention usually decreases. This is tested by giving the patient a gastric motor meal at night. If the morning aspiration contains particles of food and has a volume of 120 ml. or more, surgical intervention is necessary.

Perforation

Acute free perforation seen within 24 hours of onset is best treated surgically. Conservative management of this complication is possible when the general condition of the patient precludes operation or when surgical facilities are not available. However, surgical management offers decreased morbidity and mortality. The decision as to whether the defect should be merely oversewn or a more definitive procedure should be done must be made by the surgeon. The rationale for performing a definitive procedure at the time of acute perforation is that 40% of these patients will eventually require surgical treatment for a complication of peptic ulcer.

Hemorrhage

Approximately one fourth of all patients with peptic ulcer bleed at some time during the course of their disease.[8] Bleeding is the initial manifestation of peptic ulcer in 15% of the cases. The treatment of bleeding begins with hospitalization, correction of shock, and institution of strict medical therapy as outlined above. Anticholinergics are usually not used, because they produce atony. About one third of patients with bleeding ulcers will lose 1,000 ml. or more of blood. If the patient is seen early in the course of the hemorrhage, the initial hemoglobin determination may not reveal the extent of blood loss because of lack of time for hemodilution to occur. However, the patient's shock-like state in recumbency will make the need for blood replacement obvious. With lesser amounts of blood loss, the patient may appear fairly stable while supine. The extent of loss may be estimated by the tachycardia produced in tilting the patient to an upright position.

From the initiation of therapy the patient's condition should be followed by a surgeon. It is impossible to give hard and fast rules for determining just when surgical intervention becomes necessary, but certain general guidelines are helpful. These, along with the risk factors and clinical judgment influenced by experience, are used in the ultimate decision for a particular patient. Risk is increased if: (1) the patient is more than 45 years old; (2) this is the first hemorrhage; or (3) there is hematemesis, persistent pain, increased blood urea concentration, persistent shock, or oliguria. An important concept is the need to make this decision in the first 48 to 72 hours because of the high surgical mortality (25%) with prolonged bleeding. A general guide is to choose surgical intervention if transfusion of three to four units of blood fails to stabilize the situation in 24 hours. Other indications for surgical intervention are: (1) coexistence of obstruction or perforation, (2) recurrence of bleeding under strict management, and (3) the need to establish a diagnosis. Recent reports of the success of ligation, pyloroplasty, and vagotomy in decreasing the mortality of partial gastric resection in patients with acute bleeding are very encouraging.

The decision regarding operation in patients with chronic bouts of melena from duodenal ulcer must be individualized according to the patterns of the bleeding, patient adherence to the ulcer program, and risk factors. However, it should be emphasized that the idea that patients with chronic bouts of melena never bleed massively is not true.

Intractability

The concept of intractability in duodenal ulcer defies exact delineation almost as much as does the problem of when to operate on a specific bleeding patient. A given case may represent an intractable patient, an intractable physician, or an intractable disease. Care must be taken that the first two causes of recurrent symptoms are ruled out before operation is considered. The concept of intractability can perhaps be best presented in the words of Jones, ". . . stubborn prolongation of medical management, even when productive of temporary good remissions from symptoms until serious complications have arisen requiring more or less urgent operation, constitutes inexcusably bad medical management. . . ."[9] Intractability has been described more specifically as the failure to relieve symptoms by half-hourly feedings or as the recurrence of symptoms on ambulation. Frequently the cause of constant recurrences is the presence of subacute perforation. Evidence of this was found in 54% of patients operated on for intractability at the Graduate Hospital in Philadelphia.[10] Stubborn adherence to a medical regimen in the face of recurrent, debilitating symptoms is poor management.

Surgical Treatment of Duodenal Ulcer

An understanding by the internist of the various operative procedures[5,11] for duodenal ulcer is necessary for adequate communication with the surgeon. When ideal therapy is not available, a selection from various methods must be made to suit the individual case. Surgical interruption of gastric physiology may include elimination of the cephalic phase by vagotomy, interruption of the gastric phase by removal of the antrum, or removal of the end organ, the parietal cell mass.

Vagotomy and Pyloroplasty

In recent years the trend in duodenal ulcer surgery has been away from the two-thirds and three-fourths gastric resections and toward more conservative procedures. One reason for this is the proven effectiveness of a properly done vagotomy and drainage procedure in controlling the ulcer diathesis. Secondly, the sequelae of removal of the gastric reservoir and creation of a gastrojejunal diversion — dumping and poor nutrition — have been placed in proper perspective relative to the risk of postoperative recurrence. In many ways vagotomy and pyloroplasty approaches a more ideal technique in physiologic surgery. It removes none of the stomach and maintains intestinal continuity. Since the gastric mechanism does not appear to be overactive in duodenal ulcer, this technique preserves the alkaline secretions of the antrum. The inhibitory mechanism of the antrum and duodenum are left intact. It is a simpler operation that avoids the problems of the duodenal stump.

Partial Resection and Vagotomy

The most prominent sequelae of vagotomy are stasis and diarrhea. Compared to gastric resection, vagotomy and pyloroplasty in general gives comparable outcome (80% good results) at lower risk with less serious side effects but with an increased risk of recurrent ulcer. Nervous persons tend to have more dumping and thin persons tend to get thinner after surgical treatment. This would weight the decision toward selection of vagotomy. On the other hand, persons with high acid outputs have increased rates of recurrence; in these cases, partial resection should probably be combined with vagotomy.

Gastric Irradiation or Freezing

Other therapeutic measures in the treatment of duodenal ulcer include irradiation of the stomach and gastric freezing. The reduction of gastric acid output by irradiation of the parietal cells has a definite place in the management of the debilitated patient who is a poor surgical risk; it has also been used with some success as adjunct to medical therapy in healthier patients. Gastric freezing has no place at present in peptic ulcer therapy because of the potential hazards and the lack of demonstrated persistent relief.

Postoperative Recurrence of Ulcer

Recurrent ulcer is perhaps the most disheartening of the complications of surgical treatment. Not only is it a dangerous development but it also represents failure of a definitive attempt at cure.

Etiologic Factors

The cause of recurrent ulcer is the same as for the primary duodenal ulcer except in the Zollinger-Ellison syndrome and retained gastric antrum, both of which will be discussed later. The factors that predis-

Continued

pose to development of recurrence include: (1) site of the original ulcer (gastric ulcer rarely recurs), (2) sex (90% of recurrences are in males), (3) preoperative secretory pattern (hypersecretion), (4) extent of prior resection, (5) addition of vagotomy, (6) type of anastomosis (recurrence is increased with Billroth I), (7) duration of observation (peak recurrence after gastroenterostomy is at 11 years postoperatively while after resection it is about 3¾ years).

Diagnosis

The roentgenologic diagnosis of gastrojejunal ulcer is difficult; only about 50% can be so demonstrated. This affects recurrence rates in different series, depending on the criteria (roentgenologic or gastroscopic visualization of the lesion) in the study. However, most investigators think that the diagnosis can be made on the basis of the symptoms, especially the presence of bleeding. Some prominent features of gastrojejunal ulceration may be a more boring type of pain that is of increased severity, less well localized, and lower in the abdomen. Shorter postprandial relief and increased nausea are also characteristic. The complications of recurrent ulcer are the same as those of duodenal ulcer, but with an increased tendency to bleed (50%) and the danger of gastrojejunocolic fistula.

Treatment

Treatment of recurrent ulcer depends on the prior surgical procedure. There is general agreement that recurrence after an inadequate procedure, such as gastroenterostomy alone, would respond well to further surgical treatment. When there is recurrence after vagotomy, the integrity of the vagal pathway should be checked by an insulin test. The primary approach to treatment of gastrojejunal ulcer after partial resection is controversial. Proponents of medical management cite (1) the mortality of re-resection, (2) control by strict medical therapy in as high as 84% of cases of postoperative recurrent ulcers, and (3) published recurrence rates of 14 to 50% after a second operative procedure. On the other hand, other authors quote different series reporting very poor results of conservative management (one of 42 patients alive and unoperated on after five years). Certainly a reasonable approach would seem to be that treatment of post-gastric-resection anastomotic ulcer is usually surgical but that a trial of strict medical therapy is justified.

Retained Antrum and Zollinger-Ellison Syndrome

Recurrence of ulcer should always bring to mind the marked diathesis caused by retained gastric antrum and Zollinger-Ellison syndrome.[12] The cause of both of these conditions is continuous, uninhibited, hormonal stimulation of the parietal cell mass.

If, during the course of gastric resection, some of the antral tissue is included in the duodenal stump closure, this retained antrum will continuously elaborate gastrin because it is isolated in an alkalin medium. The treatment is surgical removal of this inadvertently retained tissue.

Zollinger and Ellison described a syndrome of intractable peptic ulcer associated with islet cell tumors of the pancreas. The extraction of the gastric secretagogue from islet cell tumors has reaffirmed the theory that the gastric hypersecretion in these patients is due to uninhibited, constant stimulation of the parietal cell mass by the tumor product. Zollinger and Ellison suggested that the preferred treatment of this disorder is removal of the end organ (total gastrectomy) because, at operation, 62% of these tumors were found to have spread beyond the pancreas. Facts helpful in the diagnosis are: (1) 25% of these cases have unusual sites of peptic ulceration, (2) 20% are associated with other adenomas, and (3) 25% include diarrhea secondary to gastric hypersecretion.

In both Zollinger-Ellison syndrome and retained gastric antrum, further support of the diagnosis is obtained by gastric analysis demonstrating near-maximal stimulation of the parietal cell mass at basal levels. In other words, the presence of a high basal acid secretion and an increase of less than 25% with maximal stimulation by histamine is suggestive of the diagnosis. The ultimate diagnostic test would be assay of secretagogue activity.

Gastric Ulcer

Approximately 25% of peptic ulcers are gastric in location. The peak incidence is one decade later than with duodenal ulcer and the sex ratio favors males by only 2 to 1. Theories of pathogenesis include, in addition to the gastrin mechanism of Dragstedt, (1) underlying antral mucosal atrophy and (2) breakdown in tissue resistance. Most gastric ulcers are located in the lesser curvature and are characterized by low-normal acid secretion. Space does not permit presentation of further clinical and epidemiologic data, but the more important factors in gastric ulceration appear to be considerably different from those of duodenal ulcer.[13] The most important fact that changes the management of gastric ulcer from that described for duodenal ulcer is the 7 to 10% incidence of carcinoma. The generally poorer response to medical therapy and the excellent results of operation also favor surgical treatment for a higher percentage of gastric ulcer patients.

In the case of the benign-appearing gastric ulcer with free acid, the "gastric ulcer ritual" must be observed. This includes hospitalization, strict medical management, roentgenologic evidence of healing, and a cooperative patient who understands the need for follow-up. All of these steps are necessary to avoid the danger of missed carcinoma in gastric ulcer. Cytology and gastroscopy are helpful, but both techniques have their share of false-positive and false-negative results. Eventually, 20 to 70% of patients with gastric ulcers will undergo gastric resection, depending on the enthusiasm of the attending physician for medical management.

Summary

The management of duodenal ulcer is generally based on what is known of the pathogenesis of the disease. Medical treatment is applicable in the majority of patients, but surgical treatment may be resorted to in an effort to change the gastric physiology. It is important to keep in mind the need for individual management of each patient and for avoidance of rigid patterns in this disease of little-known etiology.

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Marriage: the state or condition of a community consisting of a master, a mistress, and two slaves, making, in all, two. — Ambrose Bierce

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As scarce as truth is, the supply has always been in excess of the demand.
— Josh Billings

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Tumor Conference

A Changing Parotid Tumor

THE USUAL CLINICAL history of a parotid gland tumor is that a mass in the parotid steadily increases in size until the patient seeks medical attention. In over 95 parotid masses seen in the past 10 years at our hospital, only one showed a fluctuation in size. The unusual history and findings in this case illustrate a number of facts about a papillary cystadenoma lymphomatosum of the parotid gland. For convenience this tumor is usually given the eponym of "Warthin's tumor," although Albrecht and Artz[1] described three cases of it some 19 years before Warthin's description.[2]

Case Report

The patient was a 42-year-old lawyer who was admitted to the Minneapolis Veterans Administration Hospital because of a mass below his right ear.

Six years previously he had been admitted to this hospital with a 6 x 6 cm. mass at the angle of the right mandible, below the ear, presumably in the tail of the parotid gland. Eight weeks prior to this first admission, the patient had had an episode of chills and fever which he took to be a recurrence of "malaria." Two weeks later he noted the gradually enlarging mass below his ear. The enlargement continued over the subsequent six weeks. He had no pain or signs of facial nerve involvement. The leukocyte count was 8,850 with a normal differential count. A sialogram showed only beading and decrease in the size of the smaller parotid ducts, suggesting some minimal diffuse inflammation. The mass did not significantly displace any of the ducts. During the course of his work-up, the mass decreased noticeably in size without any treatment; therefore surgery was postponed. Over the next two weeks the mass continued to get smaller until at the time of discharge it was only 2 x 2 cm. in size. On the patient's return to clinic two weeks later, no mass could be found, and it was presumed that the mass had been entirely inflammatory. He was followed at three-monthly intervals for two years, during which period no mass was detected.

On his most recent admission (six years later) he had a 3 x 3 cm. mass in the same area, which had been slowly increasing in size over seven months. On examination, a 3 x 3 cm. mass could be felt in the lower pole of the right parotid gland. X-rays of the area showed a 1-2 mm. calcific density overlying the right mandible, possibly a stone.

At operation the discrete mass was found to be located in the lower pole of the parotid gland. A superficial parotidectomy was done. The surgical specimen contained a 3 x 3 x 3 cm. cystic mass with a dense connective tissue capsule. On cut section this structure contained thick mucopurulent yellowish fluid, a culture of which grew out only diphtheroids. There was a 1.5 mm. stone in one of the minor salivary ducts 1.5 cm. anterior to the mass. Frozen sections were reported to show an infected papillary cystadenoma lymphomatosum. A microscopic section of the cyst wall is seen in Figure 1. There are numerous papillary folds, pseudostratified columnar epithelium, and large areas with squamous metaplasia of the epithelium. Numerous lymphocytes are seen in the connective tissue stroma; occasional reactive follicles also appear. There

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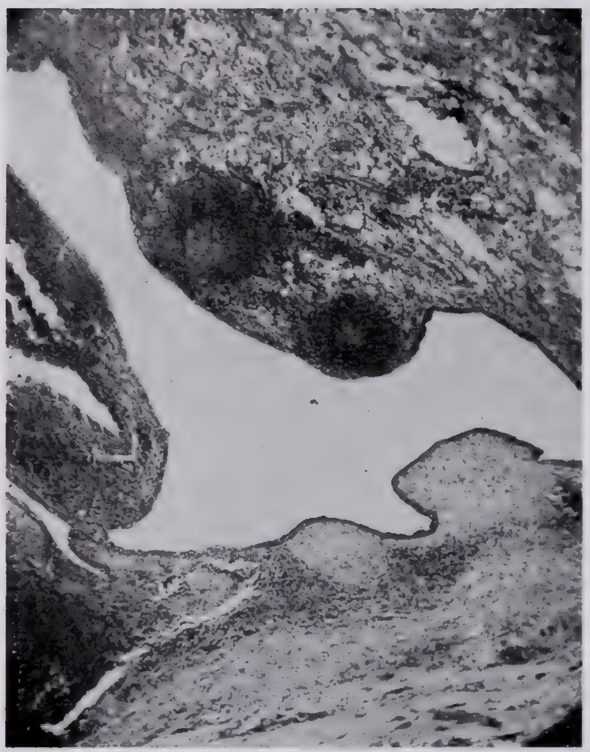

Fig. 1 — A photomicrograph of the tumor from the case discussed showing the papillary structure, the thick fibrous capsule, the diffuse inflammation, and the partial destruction of the papillary cystadenoma lymphomatosum.

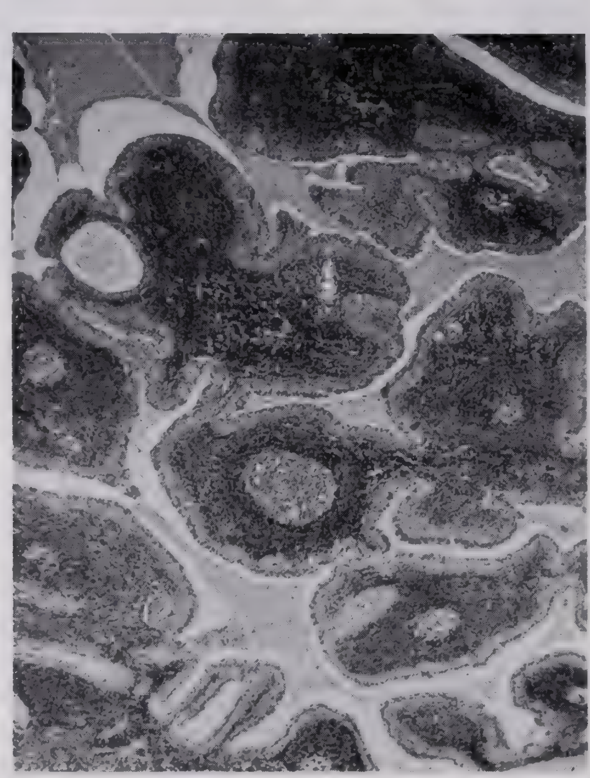

Fig. 2 — A typical papillary cystadenoma lymphomatosum from another case. The characteristic papillary structure and epithelium overlying a dense lymphoid stroma are seen. Note the reactive lymphoid follicles.

is an acute inflammatory infiltrate containing both PMNs and occasional eosinophils, the inflammation extending into the capsule. This tumor was an infected papillary cystadenoma lymphomatosum.

The patient's recovery was uneventful.

Comments

This case was interpreted as a small papillary cystadenoma lymphomatosum which has been involved in an inflammatory process on two occasions, once six years ago and again on the recent admission. The findings in both episodes are different from the typical clinical and laboratory findings of acute parotitis.

The most recent episode eventuated in an infected papillary cystadenoma lymphomatosum with partial destruction of the tumor and inflammatory infiltration of the residual tumor. Exactly what part the small ductal stone played is not clear. However, since there was some evidence of a healed parotitis in the area of the tumor, it is tempting to speculate that the localized parotitis drained to the lymphatic stroma of the tumor.

A more typical example of papillary cystadenoma lymphomatosum from another case is seen in Figure 2. The usual histology is characterized by papillary, pink, epithelial-lined cystic spaces containing pink granular material. The underlying dense blue lymphoid stroma frequently contains reactive follicles, suggestive of the functional capacity of the lymphoid tissue. The epithelium in the usual papillary cystadenoma lymphomatosum is seen on closer view (Figure 3) to have a double layer of nuclei in a pseudostratified epithelium. The nuclei nearer the surface are darker, smaller and slightly crenated. In comparing this typical picture with Figure 1, it can be seen that the inflammation has left only vestiges of the typical papillary cystadenoma lymphomatosum.

This case illustrated several facts about papillary cystadenoma lymphomatosum which are of interest.

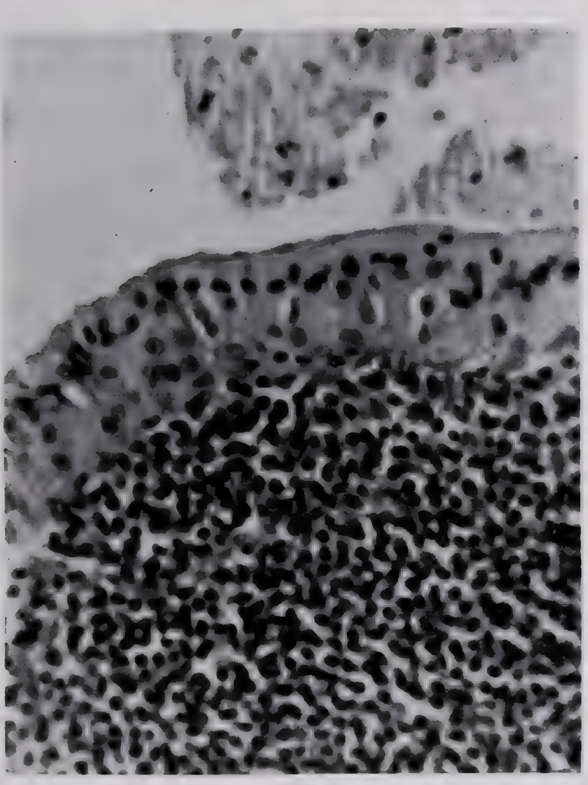

Fig. 3 — A high-powered view of the pseudostratified epithelium, showing the double layer of nuclei.

First: This tumor probably arises in salivary ductal tissue which for some reason or other becomes trapped in the functionally normal lymphatic tissue present in the tail of the parotid. This is evidenced in the frequency of reactive follicles in the stroma of a papillary cystadenoma lymphomatosum, in the occasional finding of granulomata in the tumor as well as in adjacent normal lymph nodes, and in the involvement in several cases of lymphoid stroma of a papillary cystadenoma lymphomatosum in systemic lymphomas. Thompson and Bryant have critically reviewed the histogenesis of this tumor.[3] The frequency with which ductal elements can be found in parotid lymph nodes is well known to pathologists.

Second: Papillary cystadenoma lymphomatosum is almost exclusively a tumor of males. In several large series it was found in a 10 to 1 ratio.[1,4,5] In the Minneapolis Veterans Administration Hospital population, a recent review[6] showed that papillary cystadenoma lymphomatosum was the second most common parotid tumor, comprising a surprising 25% of all parotid tumors — an incidence five times that usually reported. This incidence reflected the predominance of papillary cystadenoma lymphomatosum in males and a relative reduction in the number of pleomorphic adenomas (benign mixed tumor) encountered more fre-

Continued

quently in women. Papillary cystadenoma lymphomatosum, which has a peak occurrence one to two decades later in life than plemorphic adenoma, would also tend to be more frequent in an elderly veteran population.

Third: Papillary cystadenoma lymphomatosum is always found in the parotid gland, usually located in the lower pole of the gland.[1,6] This probably reflects the necessity of the juxtaposition of salivary ducts and lymph nodes in the origin of the tumor. The parotid gland is the one major salivary gland which has lymph nodes imbedded within its substance.

Fourth: This tumor is virtually always benign, only two well documented cases of *primary* malignancy being acceptable to a recent critical review of the malignant potential of the papillary cystadenoma lymphomatosum.[7]

The management of this tumor is that of any other parotid mass, since the papillary cystadenoma lymphomatosum has no distinguishing characteristics which will allow accurate preoperative identification and distinction from the malignant parotid tumors. Removal by superficial parotidectomy was adequate for excisional biopsy and definitive management in our cases, since all tumors were located in the lower superficial portions of the gland.

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President's Letter

Continued from page 1055.

Every delegate and every officer is familiar with the post-meeting question, "What were you fellows trying to do to us down there"? There are no "You fellows" nor any "us". There are only members of the Minnesota State Medical Association with common interests and common concerns but varying degrees of participation. Increasing that participation is the task of the Committee on Scientific Assembly; improving the participation is the acceptance by individual physicians of the soundness of Disraeli's comment.

RP Buckley M.D.

R. P. Buckley, M.D.
President
Minnesota State Medical Association

Clinical Path Conference

Recurrent Cardiac Failure Associated with Calcified Aortic Valve

Dr. Thomas E. Layman

First admission — A 73-year-old man was admitted to the hospital in a depressed state and with symptoms suggestive of duodenal ulcer. The blood pressure was 140 mm. Hg., systolic and 60, diastolic. The results of the remainder of the physical examination were within normal limits. No cardiac murmurs were heard. The patient was seen by a psychiatrist who made a diagnosis of a neurotic depressive reaction.

Roentgenographic examination of the upper gastrointestinal tract demonstrated an active duodenal ulcer. The results of the urinalysis were normal. The hemoglobin concentration in the blood was 13.6 grams per 100 ml. The leukocyte count of the blood was 6,300 cells per cubic mm. The blood urea nitrogen was 21 mg., the fasting blood glucose was 68 mg., and the total serum cholesterol was 274 mg., each per 100 ml.

During this period of hospitalization the patient was treated for the duodenal ulcer with isopropamide and prochlorperazine in the form of Combid® spansules twice daily. A second roentgenographic study of the upper gastrointestinal tract performed one month after the first demonstrated no abnormalities. Over a period of one month the patient received 12 electroshock convulsive treatments for the depressive reaction with apparently good results. He was discharged nine weeks after admission.

Second admission (*eight months later*) — The patient was again admitted for a depressive reaction and for cardiac decompensation. He complained of shortness of breath which had been present for the two weeks prior to admission. In addition, he demonstrated a depression and traits of a withdrawn personality similar to those shown during his first admission.

The results of the physical examination were unchanged from those of the first admission. A roentgenographic study of the upper gastrointestinal tract was performed and demonstrated a marked, nonobstructive deformity of the duodenal bulb. There was no demonstrable evidence of ulcer.

Continued

The results of the urinalysis were completely normal. The hemoglobin content of the blood was 12.4 grams per 100 ml. The erythrocyte sedimentation rate was 43 mm. per hour.

During his hospitalization the patient was treated with digitalis leaf and an intramuscular mercurial diuretic, in addition to Ritalin® in doses of 40 mg. three times daily and Stelazine® in doses of 5 mg. five times daily. On this regimen the patient lost eight pounds in weight, the greatest loss occurring within the first two weeks of hospitalization. No electroshock therapy was given. The patient was discharged seven weeks following admission.

Third admission (*3½ months later*) — The patient was again admitted for a depressive reaction. He had been maintained on digitalis leaf from the time of the second admission. The results of the physical examination revealed evidence of recent loss of weight. The blood pressure was 124 mm. Hg., systolic and 70 mm. Hg., diastolic. The results of the remainder of the physical examination were within normal limits. The results of the urinalysis were normal. The hemoglobin content of the blood was 12.3 grams per 100 ml. The total blood leukocyte count was 4,150 cells per cubic mm. The erythrocyte sedimentation rate was 38 mm. per hour. The blood urea nitrogen and total serum cholesterol were normal. The protein bound iodine was reported as 9.5 micrograms per 100 ml. (this test was not repeated). The erythrocyte sedimentation rate tested one week following the first was 10 mm. per hour.

During this hospitalization the patient was treated with methyl testosterone, 25 mg. per day and digitalis leaf. He was discharged from the hospital one month after admission.

Fourth admission (*three months later*) — The patient again was admitted for chronic depression and for increasing dyspnea during the prior two weeks. The blood pressure was 140 mm. Hg., systolic and 100, diastolic. A cardiac murmur was heard for the first time at the base of the heart over the aortic area and was characterized as a loud systolic murmur. Moist rales were noted at both pulmonary bases. The results of the remainder of the physical examination were within normal limits.

The patient was treated with digitalis leaf and a mercurial diuretic given intramuscularly. With this therapy he lost a total of 15 pounds, the greatest loss occurring within the first five days of hospitalization. He was discharged to a nursing home after 12 days of therapy in the hospital.

Fifth (*final*) *admission* (*13 days later*) — The patient was returned to the hospital from the nursing home because of increasingly severe dyspnea, a productive cough, peripheral edema and peripheral cyanosis. The blood pressure was 150 mm. Hg., systolic and 90, diastolic. He was markedly emaciated, dyspneic, pale and cyanotic. Examination of the thorax revealed the presence of bilateral pleural effusions; there were moist rales at both pulmonary bases. The heart rate was 80 beats per minute and regular. A loud systolic ejection murmur was heard at the base of the heart in the region of the aortic valve, and the extremities demonstrated ++ pitting edema. Except for a specific gravity of 1.005, the results of the urinalysis were negative. The blood hemoglobin content and total blood leukocyte count were normal; the blood urea nitrogen was 27 mg. per 100 ml., and the total serum protein was 7.4 gm. per 100 ml. with albumin constituting 3.3 gm. and globulin, 4.1 gm. of the total.

The patient was treated with daily intramuscular mercurial diuretics, digitalis leaf and multiple vitamins.

A right thoracentesis to remove evident fluid was attempted but was not successful.

The patient was discharged from the hospital 19 days after admission, returning to the nursing home. While in the nursing home he continued to demonstrate evidence of marked congestive cardiac failure with signs and symptoms of pulmonary congestion and pleural effusion. He suddenly expired two weeks following his discharge from the hospital.

Electrocardiograms made during the patient's first and last hospitalizations are illustrative of the many made during the course of his five admissions. Intervening electrocardiograms are transitional between the first taken (Figure 1-a) and the last taken (Figure 1-b). His first electrocardiogram (Figure 1-a) demonstrates a sinus rhythm with a P-R interval of 0.20 second. Shallow Q waves, 0.03 second in duration, are present in leads II, aVF, V_5 and V_6. In lead III, a QS pattern is present. The T waves in leads I, aVL, V_5 and V_6 are negative, while the T wave in leads II, aVF and V_4 is diphasic. The mean electrical axis is +20°.

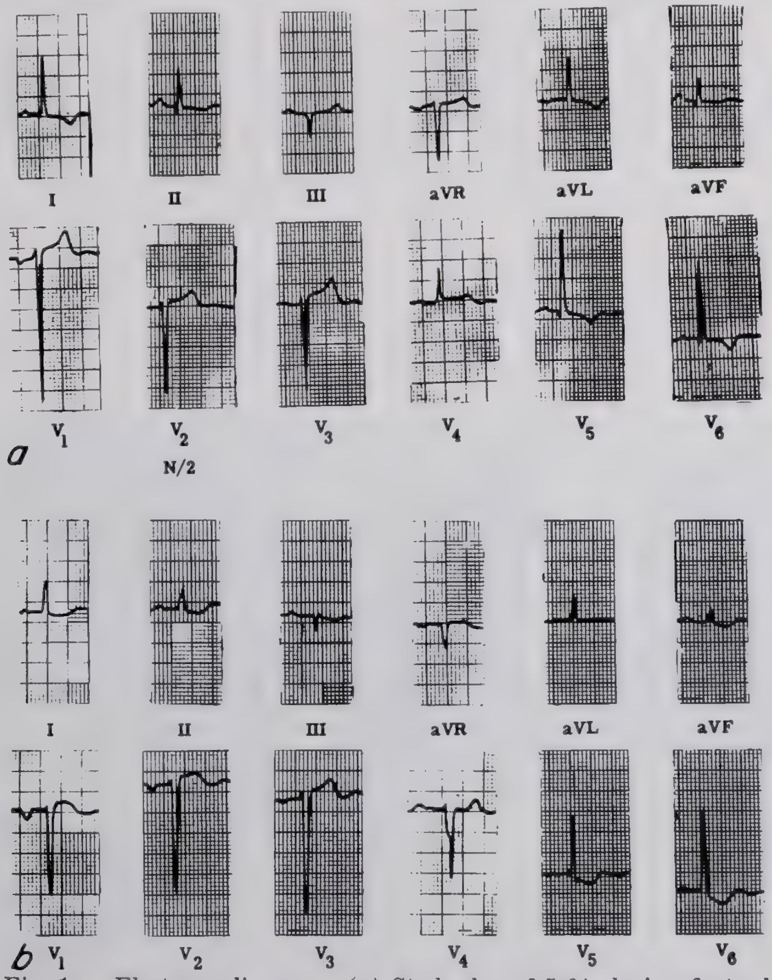

Fig. 1 — Electrocardiograms. *(a)* Study done 6-5-64, during first admission. *(b)* Study done 2-1-66, during fifth admission, ten weeks before the death of the patient.

Continued

The last electrocardiogram demonstrated sinus rhythm. In this (Figure 1-b) there was a P-R interval of 0.24 second. The small Q wave in leads II, aVF, V_5 and V_6 seen in the first admission has disappeared, while the QS pattern in lead III persists. The QRS complexes in leads II, aVF and V_4 are slurred, although the duration is normal, being 0.09 second. The T waves in leads I, II, aVR, aVF and V_1-V_6 are flattened and slightly diphasic, while minimal ST segmental sagging or elevation is apparent in the same leads. The mean electrical axis is $-5°$. At this time the P waves in leads V_1 and V_2 are wide and more negative than before.

Roentgenographic Findings

Dr. John B. Coleman

This thoracic roentgenogram, dated June 5, 1964, was made at the time of the patient's admission for a gastrointestinal problem (Figure 2). The most striking findings are the massive calcification in the aortic valvular area and the lack of much cardiac enlargement. We see that the heart is somewhat enlarged to the left and downward with a total transverse diameter of 14.7 cm. and a cardiothoracic ratio of only 42 per cent. Though the ratio is within accepted limits of normal, the impression is of some degree of enlargement. There is no evidence of left atrial enlargement. The hilar and intrapulmonary vessels are normal. The aortic caliber is also normal, and there is no unusual tortuosity. The lungs are clear. Considering the patient's age, this is a good looking thorax, except for the calcification and slight cardiac enlargement.

The rest of my comments pertain to selected films from subsequent admissions up to the time of the patient's death (Figure 3). On April 28, 1965 (Figure 3-a), the hilar and intrapulmonary vessels are generally enlarged, consistent with left heart failure, and the lower third of each pulmonary field is so dense that the cardiac outline and the diaphragm are obscured. There is fluid in both pleural spaces, more on the right than

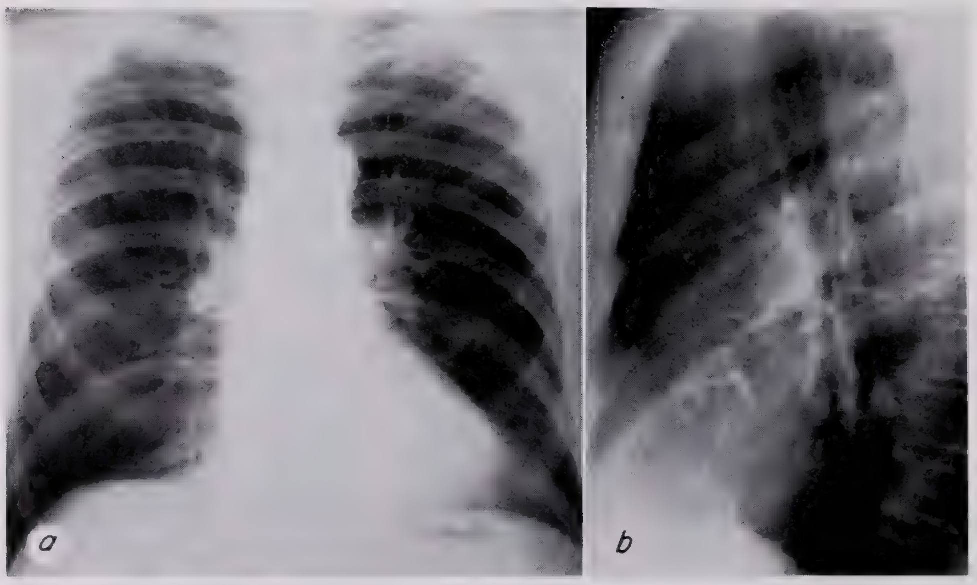

Fig. 2 — Thoracic roentgenogram made during the first admission (6-5-64). *(a)* Frontal view and *(b)* Lateral view. Calcification of the aortic valve. A calcific spur extends to the anterior region of the mitral valve.

on the left. Pulmonary consolidation is also present, and, while we may expect that it is accounted for in part by edema, we must consider in our differential the possibility of bilateral basilar pneumonia, atelectasis, or massive infarction. The heart is not likely greatly enlarged in spite of the severe degree of the other findings; this may reflect recent digitalization, but it also makes us wonder whether some associated cause such as renal failure may contribute to the vascular congestion and effusion.

In 1966, a film made on February 1 (Figure 3-b) reveals similar marked density of the lower pulmonary fields with bilateral effusion, which is greater in amount than before. Again we are impressed that the heart is not greatly dilated, though we cannot, of course, outline it distinctly. In the periphery of the lower aspects of the lung, we see the horizontal lines of congested lymphatic channels which help us so often in the diagnosis of chronic cardiac failure. I would estimate that the liver is not enlarged enough to elevate the right leaf of the diaphragm. On February 8 (Figure 3-c) the density in the bases of both sides of the thorax have largely disappeared; fluid remains in the right pleural space. The lungs have an appearance of over-distention, and there is no vascular overfilling as might result from left-sided cardiac failure. The heart is not larger than it was in 1964. Now for the first time, we observe a triangle of dense pulmonary tissue with its base appearing at the right hilum. In the lateral view this was shown to represent the middle lobe. The findings are characteristic of almost total collapse of the lobe. There is nothing else to indicate its cause, whether due to obstruction or to shrinkage from a chronic intrinsic disease process.

Our last roentgenographic examination was performed on March 14, 1966, and the findings were similar to those apparent six weeks earlier (Figure 3-b). The bases were extremely dense, the heart and diaphragm obscured and the peripheral pulmonary vasculature perhaps slightly increased.

Discussion

Dr. James N. Karnegis

The major symptoms as given in the protocol appear to be of psychiatric, gastrointestinal and cardiac natures. There is no informa-

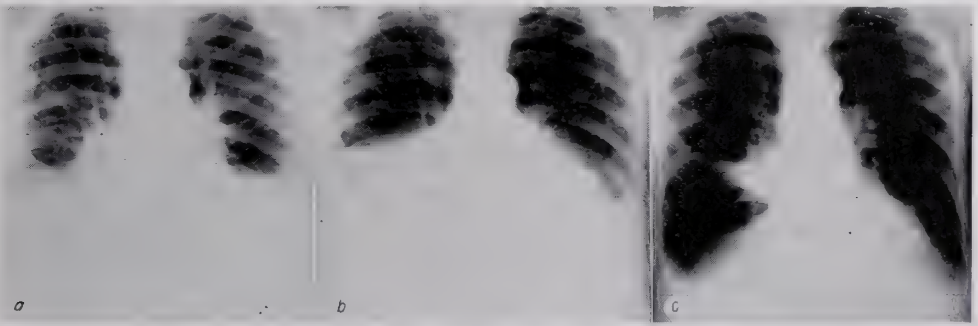

Fig. 3 — Thoracic roentgenograms made subsequent to first admission. *(a)* (4-28-65). Approximately eleven months subsequent to the roentgenograms shown in Figure 2. *(b)* (2-1-66). Roentgenogram made approximately nine months after that shown in *a*. *(c)* (2-8-66). Roentgenogram made about one week after that shown in *b* and approximately nine weeks prior to the death of the patient.

Continued

tion regarding this elderly man's past history so that we do not know if he had had psychiatric or other difficulties prior to his first admission, nor do we know anything about his state of health in the past.

There was ample evidence on the first admission to indicate cardiac disease. The aortic valve was calcified on thoracic roentgenography. The first electrocardiogram showed left ventricular hypertrophy with strain. Later, the patient was dyspneic, showed an increased cardiac shadow, pulmonary congestion and pleural effusion. He lost weight and improved on diuretics. The pattern, however, repeated itself until on the last admission there were cyanosis, edema, pleural effusion and a basal systolic ejection murmur. This course continued until death.

These considerations seem to lead to the inescapable conclusion that the patient had calcific aortic stenosis. The etiology of the aortic valvular disease could be rheumatic. However, since there is no evidence of mitral valvular disease, the lesion could be the result of a congenital deformity, such as a bicuspid aortic valve.

The calcific aortic stenosis may have been associated with other complications. The murmur was not heard until the last two admissions. It is possible that it might have been repeatedly missed, but changing murmurs suggest bacterial endocarditis. There is, however, no support for that possibility in the information given. Pleural effusion and pulmonary infiltration occurred. We recognize that chronic congestive cardiac failure predisposes to the development of pulmonary emboli. It is known that myocardial infarction is rare, even in severe aortic stenosis, unless there is coexistent coronary arterial disease.

Although the diagnosis of calcific aortic stenosis seems secure, there are many unusual features. It is true that some patients with this lesion live beyond 70 years of age, but most become symptomatic in the fifth and sixth decades. The typical blood pressure of severe aortic stenosis is not described. The valve was heavily calcified, as seen in the roentgenogram, and it seems curious that auscultation apparently persistently failed to reveal any of the characteristic findings of stenosis of the aortic valve. Also, the total elapsed time from the onset of cardiac failure to death was only about seven months. This indicates a very precipitous course if resulting from aortic stenosis, since the average survival time after the onset of congestive cardiac failure in this disease is usually about two years.

The pulmonary findings are also unusual for aortic stenosis. Cardiomegaly and pleural effusion are consistent with that lesion, but the parenchymal infiltrate and collapse of the right middle lobe do not fit very well.

It is difficult to explain the psychiatric and gastrointestinal symptoms on the basis of the patient's aortic stenosis. Of course, they may be entirely unrelated. But the usual cerebral symptom of tight aortic stenosis is syncope, and that was not present in this case. Furthermore, both the mental depression and the abdominal symptoms antedated the clinical appearance of the cardiac disease. In addition, the elevated erythrocyte sedimentation rate remains unexplained.

The picture is not entirely consistent with the diagnosis of calcific aortic stenosis alone. It seems that we must also consider the possibility that the patient had some additional disease process. Although we do not know anything about the man's past psychiatric history, we do know that his mental state was a severe problem in his last 15 months of life. The development of mental changes and/or epileptic seizures in the adult should always suggest the necessity of ruling out a cerebral tumor. It is well known that lesions of the frontal lobe of the brain, although difficult to diagnose early, may cause the patient to present with psychiatric symptoms. If this patient did have a brain tumor, it would be more likely metastatic than primary, since pulmonary and abdominal symptoms were also present. The bronchi are the most common source for tumors which metastasize to the brain. There is some suspicion of a bronchogenic carcinoma, since the middle lobe was collapsed. Metastatic carcinoma could explain the pleural effusions and pulmonary infiltrates. The second electrocardiogram shows a diminished voltage as well as a change in the QRS patterns. The Q waves are lost in leads II, aVF, and in the precordial leads, and a splintered complex is present in leads II and aVF. These findings would be consistent with extension of a tumor to the heart and pericardium and with the presence of pericardial effusion. Metastases to the liver and the abdominal cavity would explain the gastrointestinal symptoms and the reversed A/G ratio. The marked cachexia is entirely consistent with a rampaging malignancy. An elevated erythrocyte sedimentation rate is commonly found with cancer, and it can return to normal in the presence of congestive cardiac failure. The value for protein bound iodine in the blood is high and, if correct, remains unexplained. There is no other evidence for thyrotoxicosis. Isopropamide does not cause elevated blood levels of protein bound iodine when determined by the ash method.

Another possibility that must be mentioned is that a primary tumor could have arisen in the abdomen. A gastric or pancreatic carcinoma with metastases to the lungs, heart and brain would be consistent with the findings. This, however, is less likely than a bronchial carcinoma, since the latter is the most common tumor to metastasize to the pericardium and heart. A definite diagnosis of a malignancy cannot be made from the available information, but the suspicion that one is present must be entertained.

In conclusion, it seems clear that the patient had calcific aortic stenosis, perhaps on the basis of a congenital deformity, such as a bicuspid aortic valve; metastatic carcinoma must be considered and cannot be excluded by the data. If a malignant tumor were present, the primary would most likely have been a bronchogenic carcinoma.

Dr. Layman

The patient exhibited depressive behavior for about 20 years prior to the first admission described.

Dr. Karnegis

With the information just presented, I would be less inclined to consider an organic cerebral lesion, and, in turn, this makes somewhat less likely the possibility of a malignant tumor being present in this case.

Dr. Layman

Dr. Edwards, would you present the necropsy findings and close the discussion.

Continued

Dr. Jesse E. Edwards

The pathologic findings of significance included lesions in the heart, features of congestive cardiac failure and changes in the right lung. No tumor was present.

The heart was grossly enlarged, weighing 660 grams. The main basis for the enlargement was left ventricular hypertrophy. Three areas in the heart were of particular interest, namely, the aortic valve, the mitral valve and the papillary muscles of the left ventricle. The aortic valve displayed a fixed and narrowed orifice having a "tear-drop" shape and measuring 1.8 cm. in length and 0.7 cm. at its greatest wall. The abnormalities of the aortic valve were derived from the presence of a congenital malformation and secondary acquired calcification. The congenital malformation of the valve was in the form of a unicommissural, unicuspid valve (Figure 4). Superficially resembling a congenital bicuspid state, the aortic valve was equipped with but one commissure and one cusp. This became apparent when one started at one side of the commissure and proceeded along the cusp. As the cusp approached the aortic wall opposite the commissure, it turned upon itself and proceeded toward the commissure where it inserted to complete the single commissure. Opposite the commissure a broad calcified raphe extended from the aortic wall onto the cusp. A second, less bulky raphe was also present. I have designated this type of aortic valvular deformity as a unicommissural, unicuspid valve.[1] It has the characteristics of being intrinsically stenotic as, except for the single commissure, the valve resembles the dome-shaped valve of congenital pulmonary stenosis. Qualitatively the valve is like that which is usually present in symptomatic congenital pulmonary valvular stenosis. In the case presented in this conference the orifice of the malformed valve was relatively wide and consequently may not have been significantly malfunctional until calcium became deposited in it. The calcium was heavily deposited in the valvular substance and a large spur of calcium extended downward onto the ventricular aspect of the anterior mitral leaflet.

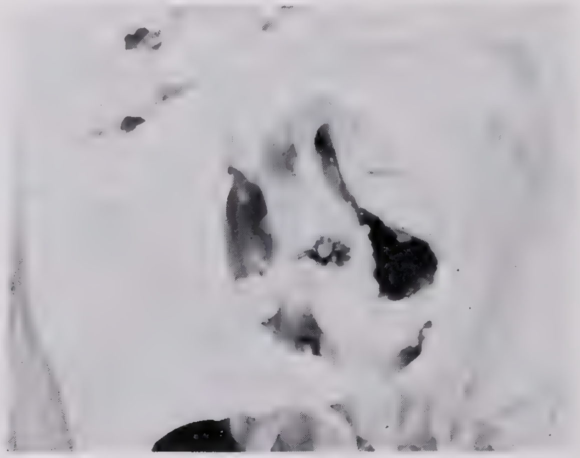

Fig. 4 — Aortic valve from above. The structure is that of a modified dome (unicommissural, unicuspid aortic valve) with secondary calcification. The orifice is markedly restricted in size and exhibits a "tear-drop" shape.

With the acquisition of calcific deposits, the aortic valve became rigid. This may have increased the degree of obstruction, and it may also have introduced an element of aortic insufficiency. The latter point is explained as follows. In the stages when the valve was fibrous, its relatively freely movable structure may have prevented incompetence by elements of the dome-shaped tissue impinging upon themselves to effect a flutter-valve action. With rigidity developing on the basis of calcification, the latter function was probably lost, yielding a stenotic valve with a fixed orifice. The consequence of the acquired aortic insufficiency was to accentuate the degree of aortic stenosis. This assumption is based upon the principle that the degree of stenosis of a valve is determined not only by its absolute caliber but also by the amount of blood flowing through the valve in a given period of time. Obviously, for a given volume of forward flow, more blood passes through the aortic valve during systole when aortic insufficiency is present than when the aortic valve is competent.

The mitral valve was also the site of a malformation with secondary acquired disease (Figure 5). This was characterized by a solitary accessory chorda tendinea which had extended from the ventricular septum to the ventricular aspect of the center of the anterior leaflet. At the time of our examination of the heart at necropsy, this chorda was found detached near its septal attachment. The free end of the chorda was tapered and discolored tan, a picture of acquired rupture. Histologically, no signs of bacterial infection were evident. The evidence suggests that the presence of the accessory mitral cord and its acquired rupture had probably played only minor, if any, roles in causing any disturbance of the circulation. The position of the accessory cord corresponds with the position of accessory cords that attach to the cleft anterior mitral leaflet in the malformation known as persistent common atrioventricular canal.[2] In this case with intact valvular leaflets and the usual papillary muscle and cordal mechanisms, one cannot attribute any useful function by the anomalous cord when it was intact. In that state the cord could only have been detrimental by causing unusual restraint upon the anterior leaflet and being responsible for mitral insufficiency. The clinical and

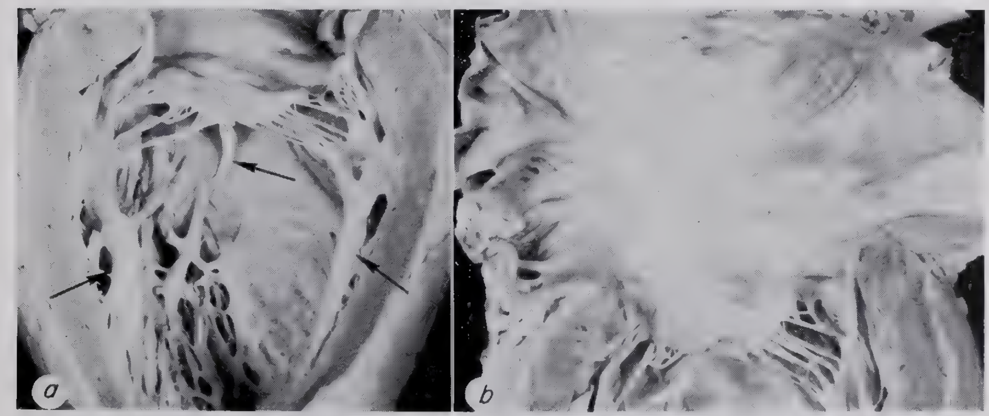

Fig. 5 — *(a)* Left atrium and left ventricle exposing the mitral valve. From center of the anterior leaflet of the mitral valve an anomalous cord (point of upper arrow) extends toward the ventricular septum from which it had ruptured. In addition to left ventricular hypertrophy, the papillary muscles (lower arrows) are atrophic on the basis of infarction and secondary scarring. *(b)* Left atrium and mitral valve. The cord shown in *a* is partly out of view. The basic support of the mitral valve through the two papillary muscles is normal, although atrophy of the papillary muscles is present. The left atrium is dilated.

Continued

pathologic evidence does not suggest that this patient suffered from primary mitral insufficiency throughout his life. Moreover, one cannot envision rupture of the anomalous mitral cord being responsible for any loss of essential restraint upon the mitral valve in view of the presence of the usual cords and papillary muscles. One must accept the presence of the anomalous mitral cord and its rupture as interesting, yet functionally unimportant features in this case.

Quite another matter pertains to the papillary muscles. The papillary muscles of the left ventricle were atrophic on the basis of loss of muscle and replacement by scar tissue (Figures 5 and 6). This change, which is considered to be the result of infarction of the papillary muscles, occurred in the absence of any coronary atherosclerosis. The coronary arteries were singularly devoid of any such lesions! Fragmentation of the diseased aortic valve may occur and lead to embolism within the myocardium and in other sites supplied by the systemic circulation. No such lesions were found to explain the infarction of the papillary muscles in this case.

We are strongly inclined to attribute the infarction of the papillary muscles in our case to the left ventricular hypertrophy associated with aortic valvular disease. The basis for this opinion resides in our observations that in the presence of hypertrophy of the left ventricle and in spite of normal coronary arteries, the left ventricular papillary muscles exhibit a strong tendency to infarction. In studies by Moller and associates from our institutions, infarction of papillary muscles and secondary mitral insufficiency were commonly observed in infants with symptomatic congenital aortic stenosis.[3,4] Extension of these studies by Drs. Ernesto Arosemena, James Moller and myself to adults with left ventricular hypertrophy of various causes show a predilection for infarction of the papillary muscles of hypertrophied left ventricles.[5]

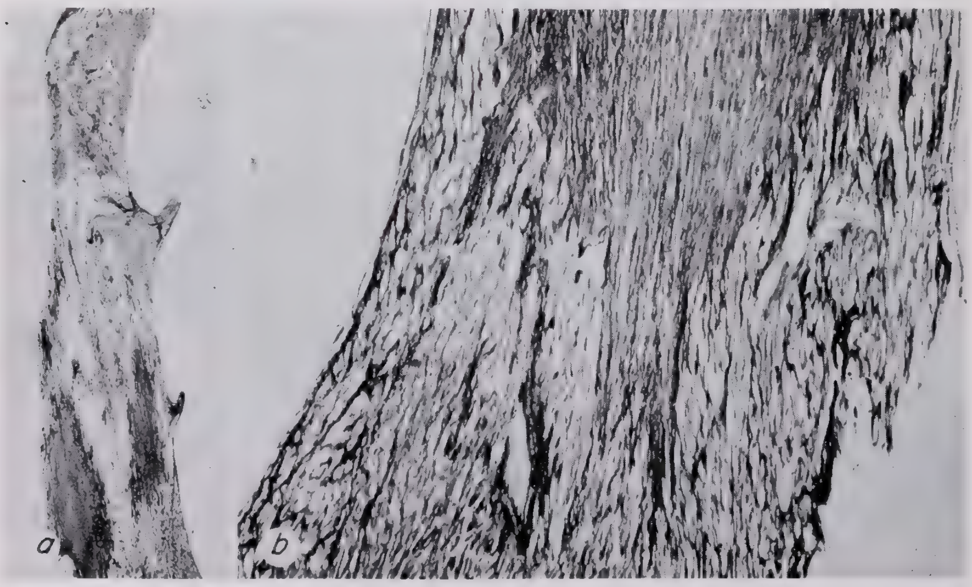

Fig. 6 — Photomicrographs of posteromedial papillary muscle of the left ventricle. *(a)* Low-power view shows extensive zones of scarring (black) resulting from infarction. Infarction is also focally present in pale areas. Elastic tissue stain; X 5. *(b)* Close-up view of junction of scar (black) and noninfarcted muscle at the base of the papillary muscle. Elastic tissue stain; X 25.

Infarction of papillary muscles, whether complicating coronary arterial disease or left ventricular hypertrophy, may cause mitral insufficiency.[6] Enlargement of the left atrium in this case may be taken as a probable anatomic sign of mitral insufficiency. We should conclude that the latter process had resulted from the observed infarction of the papillary muscles.

The middle lobe of the right lung was consolidated. Histologically it showed a picture of alveolar hemorrhage and focal scarring consistent with healed infarction.

Diagnosis

Calcification complicating congenital unicuspid aortic stenosis with secondary infarction of papillary muscles of left ventricle.

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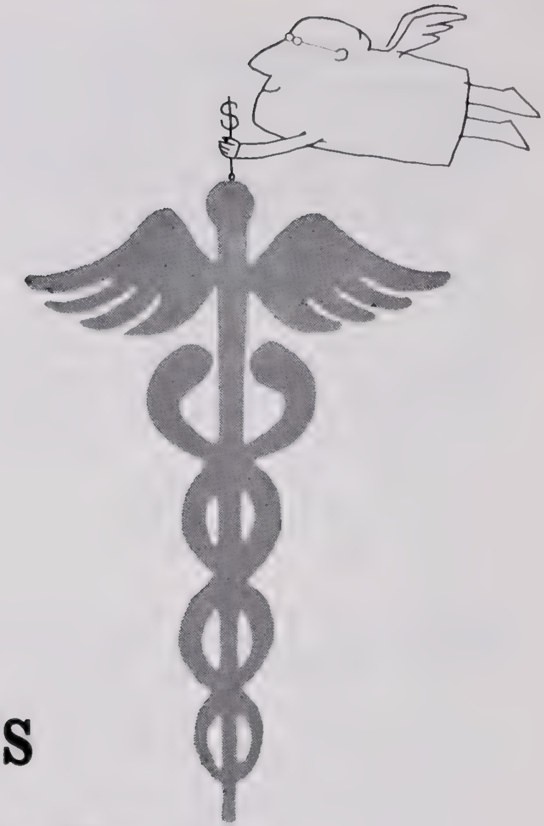
On Wine From Sanitatis Salernitanum

White Muskadell, and Candie wine, and Greek,
Do make men's wits and bodies grosse and fat;
Red wine doth make the voyce oft-time to seeke,
And hath a binding qualitie to that;
Canarie, Madera, both are like
To make one leane indeed; (but wot you what)
Who say they make one leane, would make one laffe,
They meane, they make one leane upon a staffe.
Wine, Women, Baths, by Art or Nature warme,
Us'd or abus'd do men much good or harme.

When death consents to let us live a long time, it takes successively as hostages all those we have loved. — Ninon de Lenclos



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Grand Rounds

Hypertensive Crisis and Tranylcypromine (Parnate)

JOHN CROSSON, M.D.
Medical Resident

TRANYLCYPROMINE (PARNATE) is one of the many monoamine oxidase inhibitors presently being used for the treatment of depression and hypertension. In the early 1960s there were several reports in the British literature of severe hypertensive reactions, some fatal, in patients taking tranylcypromine.[7,9] In 1964, because of these reports, tranylcypromine was removed from the American market for several months. However, it was later returned for clinical use with the idea that it would be safe if proper precautions were taken. To understand the pathophysiology underlying the hypertensive reactions it is necessary to understand the chemistry of monoamine oxidase and the inhibitors of this enzyme.

Chemistry

Monoamine oxidase is an enzyme that catalyzes the oxidation of amines to the corresponding aldehyde, peroxide and ammonia.[1] This enzyme was first demonstrated in conjunction with the metabolism of tyramine in 1928 by Hare.[2] He demonstrated an enzyme, which he called tyramine oxidase, which catalyzes the deamination of tyramine to the corresponding aldehyde and ammonia. This is the same enzyme that deaminates epinephrine and norepinephrine as well as other amines.[3] The amino group must be attached to a terminal carbon atom to be metabolized by this enzyme. Thus ephedrine and amphetamine are not acted on by monoamine oxidase.[3]

History

Monoamine Oxidase Inhibitors

In the early 1950s iproniazid and isoniazid were found to be effective

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*Presented as a Medical Grand Rounds at Hennepin County General Hospital, Minneapolis, April 5, 1966.

Continued

in the treatment of tuberculosis. Iproniazid is a monoamine oxidase inhibitor but isoniazid is not. In a study comparing the relative potency of these two drugs, Ogilvie described the first hypertensive crisis with monoamine oxidase inhibitors. He observed 42 patients with tuberculosis treated with iproniazid and 47 treated with isoniazid and found toxic reactions in 30 of 42 on iproniazid and in only seven of 47 on isoniazid. He described attacks of severe headache, palpitations, flushes, sweats and hypertension in four of the patients on iproniazid and therefore concluded that iproniazid was more effective in treating tuberculosis, but also much more toxic than isoniazid.[5] Iproniazid was later taken off the American market because of hepatotoxicity.

In 1960 Lurie and Salzer described attacks of severe headache and a marked rise in blood pressure in two of 84 patients taking tranylcypromine.[6] Lees and Burke observed similar attacks in 11 of 60 outpatients taking the drug. They described these as attacks of palpitation, throbbing pain in the head, dyspnea, bradycardia, sweating, and vomiting. Interestingly, they observed, before the mechanism was known, that these attacks were similar to those in patients with pheochromocytoma.[7]

Tyramine in Cheese

In a letter to the editor, Blackwell relates that he had been told by a pharmacist friend of his that the pharmacist's wife, who was on parnate, had attacks of headaches and hypertension after eating cheese.[8] Blackwell was skeptical, but he took dietary histories on 12 of his patients who had hypertensive crises while on monoamine oxidase inhibitors. He felt that the history was unreliable in two; but of the other ten, he found that eight had eaten cheddar cheese within one-half to two hours before the onset of the attack. One of the others had eaten Marmite, a sandwich spread later shown to produce these attacks. His description of the attacks is remarkably similar to that described by our patient. The attack begins with a forceful heart beat (palpitation), followed by a pulsating of the vessels in the neck. Soon a choking sensation and sweating develop, followed by a throbbing headache in the occipital and temporal region. The headache lasts one to three hours. On examination both systolic and diastolic hypertension as well as bradycardia is noted. Three of his 12 patients had intracranial bleeding.[9]

The importance of cheese was pointed out by Bethune et al. in their retrospective study. They reviewed the records of 126 outpatients treated with monoamine oxidase inhibitors prior to September 7, 1963, and found 23 episodes of hypertension and headaches for an incidence of 18.2 per cent. On September 7, 1963, they started warning their patients of the dangers of cheese with monoamine oxidase inhibitors. After this date, 244 patients were treated with monoamine oxidase inhibitors, and there were only eight hypertensive episodes for an incidence of 3.3 per cent. In five of these eight the warning had not been heeded.[10]

Mendels, however, recorded the blood pressure weekly in 150 patients on parnate, followed for 15 months, and he found no episodes of hypertension.[11]

Asatoor was the first to implicate tyramine in cheese as the cause of these hypertensive crises. He reviewed the previous reports showing that tyramine is present in significant amounts in some cheeses. He then measured the amount of tyramine in Camembert cheese and found it to be 0.2 per cent. He fed Camembert cheese to normal subjects and measured the urinary excretion of p-hydroxyphenylacetic acid, a compound formed from tyramine by the action of monoamine oxidase and aldehyde oxidase. He found a 200-per cent increase in the urinary excretion of this acid in two hours, indicating that the tyramine in the cheese is absorbed and subsequently metabolized. He then proposed that monoamine oxidase inhibitors would inhibit the metabolism of tyramine, allowing it to circulate in an active form.[12]

Blackwell and Mabbitt measured the tyramine content in certain cheeses and found that some of the English cheddar cheeses that had been shown to produce hypertensive crises had tyramine contents ranging from 480 to 953 mcg. per gram of cheese. The tyramine content was seen to vary a great deal from cheese to cheese and to be nonexistent in some. Tyramine is produced by the action of bacteria on tyrasine; so the shorter the time required to ripen the cheese the less tyramine is present.[13] New York cheddar cheese has a high concentration of tyramine. The only alcoholic beverage that has tyramine is Chianti wine.[14] Marmite, a yeast extract, has 1,500 mcg. tryamine per gram. As little as 4 grams of Marmite in a person taking monoamine oxidase inhibitors has been shown to produce hypertensive reactions.[15]

Horwitz found that tyramine was 10 to 100 times as effective in raising blood pressure after monoamine oxidase inhibitor administration. He studied seven patients with essential hypertension who had normal blood pressure in the hospital. He gave them intravenous tyramine in doses enough to raise the blood pressure 25 to 65 mm. Hg. In controls he found it took an average of 80 mgm. per hour, but in monoamine oxidase inhibitor-treated patients only 1.3 mgm. per hour to raise the blood pressure. Orally 250 mgm. tyramine produced a rise of 35 mm. Hg. in blood pressure in controls and 6 mgm. produced a significant rise in treated patients.[16]

Thus as little as 10 grams of cheese that contains 1 mgm. of tyramine per gram could easily produce hypertension in patients on monoamine oxidase inhibitors.

Tyramine presumably acts by releasing norepinephrine from the sympathetic nerve endings, so causing the hypertension.[17]

Catecholamine Metabolism

In order to further understand the role of tyramine and monoamine oxidase inhibitors in producing hypertensive crises it is necessary to understand how catecholamines are stored and metabolized. There are two major pathways for the metabolism of catecholamines: one utilizing an enzyme called catechol-o-methyl transferase and the other utilizing monoamine oxidase. The catechol-o-methyl transferase pathway is the major pathway for the metabolism of catechol amines in man;[18] however, monoamine oxidase does play an important role. It is known that treatment in experimental animals with monoamine oxidase inhibitors leads to increased brain norepinephrine, even though the metabolism of exogenously administered norepinephrine is unaffected by these drugs.[18] It is currently accepted that norepinephrine is stored in several different ways in the neuron:

1. Stored in small granules in the cell in combination with adenosine

Continued

triphosphate — the stable pool.

2. Stored in the same granules but not combined with adenosine triphosphate — the mobile pool.

3. Stored outside the granules close to the terminal cell membrane and released by nerve stimulation.[4]

The Table shows that these different sources of norepinephrine are affected differently by monoamine oxidase. It is currently thought that monoamine oxidase, which is found in the mitochondrial fraction of the cell, acts only on intracellular norepinephrine and that catechol-o-methyl transferase is responsible for metabolism of norepinephrine once it is released from the cell. Thus nerve stimulation releases active norepinephrine into the synaptic junction where it exerts an effect, then is metabolized by catechol-o-methyl transferase. Similarly, tyramine acts by releasing the mobile fraction of norepinephrine directly into the circulation in an active form where it too is acted on by catechol-o-methyl transferase. Conversely, reserpine acts on the stable pool, releases norepinephrine from the granules intracellularly where it can be metabolized by monoamine oxidase and released into the circulation in an inactive form.[19] This explains why reserpine and tyramine, which both act by depleting peripheral stores of norepinephrine, have opposite actions. That tyramine and nerve stimulation affect different sources of norepinephrine has been shown by the fact that sympathetic nerve stimulation is carried on in the normal fashion even when norepinephrine has been maximally released by tyramine.[20] When monoamine oxidase inhibitors have been given, followed by reserpine to release norepinephrine, this released norepinephrine cannot be metabolized intracellularly as it normally would be; so it is released in an active form into the circulation.[19] This is born out experimentally in several different laboratory animals which show marked excitation instead of the usual depression with reserpine if they had previously been pretreated with monoamine oxidase inhibitors.[21]

The effect of tyramine in patients who have been on monoamine oxidase inhibitors is probably two-fold. First of all, monoamine oxidase is found in high concentration in the liver and intestines,[1] so that it is important in metabolizing administered tyramine. When this enzyme is inhibited, the tyramine circulates in the entire body in an active form. Secondly, monoamine oxidase is important in the intracellular metabolism of norepinephrine, so that when this enzyme is inhibited there is a buildup of

TABLE*

Norepinephrine Source	Metabolized by Monoamine Oxidase	Effect of Monoamine Oxidase Inhibitors
Administered	+	+
Circulating	±	0
Mobile pool	±	0
Stable pool	++++	++++
Nerve stimulation	0	0
Drug released		
Tyramine	0	0
Amphetamine	0	0
Reserpine	++++	++++
Quanethidine	+++	+++
2 Methyl dopa	+++	+++

*Kopin, J., and J. Axelrod: Ann N Y Acad Sci 107:848, 1963.

norepinephrine in the cells, part of which probably goes into the fraction released by tyramine, so that there is more norepinephrine to be released.

There is good evidence that the hypotensive effect of monoamine oxidase inhibitors is not related to the inhibition of this enzyme at all. Gessa and his co-workers feel that monoamine oxidase inhibitors act directly to prevent release of norepinephrine by sympathetic nerve impulses.[22]

Treatment

Workers have long noted the similarity between hypertensive crises with monoamine oxidase inhibitors and attacks associated with pheochromocytomas. The previous information on the mechanism of production of these hypertensive crises would suggest that the best treatment would be the use of alpha adrenergic blocking agents such as phentolamine.[1] In large series this has proven to be very effective in doses of 5 mgm. intravenously given carefully with frequent blood pressure checks until the pressure is in normal range.[10] Dibenzyline in dosage of 10 mgm. orally has also been used successfully.[10] On theoretical and experimental grounds reserpine should be avoided, as one might expect this drug to produce even greater increase in blood pressure. However, Moser and his co-workers, in studying the effects of isocarboxazid and reserpine in 43 hypertensive patients, found that there was no increase in blood pressure when reserpine was given to patients previously treated with the monoamine oxidase inhibitor.[23]

It should be pointed out that other drugs are potentiated by the use of monoamine oxidase inhibitors; these include narcotics, alcohol, barbiturates, insulin and tranquilizers. Particular care must be taken in using demerol in patients on monoamine oxidase inhibitors, as severe hypotension and respiratory depression have been seen with small doses of demerol. Also severe reactions of hypertension, seizures and hyperpyrexia have been seen using monoamine oxidase inhibitors and imipramine (Tofranil) at the same time.[1]

Case Report

A 53-year-old, white female nurse was hospitalized in December, 1965, with the chief complaint of headache and palpitations. She had a 10-month history of mild hypertension and was on tranylcypromine (Parnate) 10 mgm. b.i.d. and trifluoperazine (Stelazine) 2 mgm. b.i.d. The patient had felt essentially well until 6:45 p.m. of the day of admission when she experienced the sudden onset of palpitations, followed quickly by a severe occipital headache which progressed to a generalized headache. She took her pulse at that time and found it to be 52 per minute. She had difficulty seeing but finally was able to call for help.

When seen in the emergency room her blood pressure was 240/110. There was no vomiting but some nausea. On questioning, she said she had eaten some cheddar cheese soup 30 minutes prior to the onset of symptoms. This was the first time she had ever eaten this type of soup.

On admission to the ward her blood pressure was 210/140/90 and her pulse was 50 and regular. She did not appear acutely ill. Pupils were equal and reacted. Funduscopic examination was unremarkable. Neck was supple. Chest and abdomen were normal. Neurological examination was within normal limits. EKG showed only sinus bradycardia. Urinalysis and hemogram were normal. Skull films and chest x-ray were normal. The patient was treated with one 25 mgm. dose of apresoline, analgesics and bed rest. By the following morning her blood pressure was in normal range. By the second hospital day her headache was gone and she was discharged on the third day.

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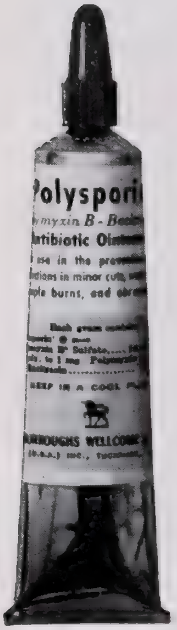

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Advances

Antibacterial Management of Infection Due to Gram-Negative Bacilli*

Part III. Use of Ampicillin, the Cephalosporins, Spectinomycin, and Chemotherapy

WILLIAM J. MARTIN, M.D.**
Rochester, Minnesota

Ampicillin

THE CORE of the penicillin molecule is 6-aminopenicillanic acid; differences among the penicillins depend on the nature of side chains attached to the core. By inhibiting the production of the mold, *Penicillium chrysogenum*, at the point at which only the unattached core has been produced, new penicillins have been semisynthesized, which reflect variations in the attached side chains. Ampicillin, which has an aminobenzyl side chain, is an example of a penicillin with this ability.

Ampicillin (Polycillin, Penbritin) is given orally or parenterally and is bactericidal against strains of *Escherichia coli, Proteus mirabilis, Salmonella, Shigella, Haemophilus influenzae* and *H. parainfluenzae, Brucella,* and some species of *Bacteroides.* However, it is ineffective against most *Proteus* organisms that are indole-positive and against *Klebsiella-Aerobacter* and *Pseudomonas* organisms. The emergence of resistant strains of *E. coli* and *Proteus* has been described in patients receiving ampicillin.

Ampicillin is not active against penicillin G-resistant staphylococci. The drug is somewhat less active than penicillin G against pneumonococci, streptococci, and *Neisseria,* and *Clostridium* organisms.

Results comparable to those obtained with previously available agents have been described in enteritis from *Shigella* and *Salmonella* organisms. However, some strains of *Salmonell*a are resistant to ampicillin on in-vitro testing. Fecal or urinary excretors of *Salmonella* organisms are more likely to respond to ampicillin than are biliary excretors. The response of biliary excretors in patients without cholelithiasis is better than it is in those with stones, but after cholecystectomy about 50% of the latter patients may be successfully treated. As yet, ampicillin has not displaced chloramphenicol as the drug of choice in typhoid fever. Urinary infections caused by *E. coli, P. mirabilis,* and enterococcus organisms have responded to ampicillin. Ampicillin has eradicated *Haemophilus influenzae* from the respiratory tracts of patients having chronic bronchitis and has been effective in pneumonia and meningitis caused by *H. influenzae.*

Dosage

Usually 250 and 500 mg. of ampicillin is given every four to six hours by the oral route. In serious infections, such as typhoid fever, 4 to 6 gm. is given daily until the fever has subsided, when the dosage may be reduced to 2 to 3 gm. daily for a total period of treatments of three to four weeks; however, some investigators have given typhoid carriers the higher dosage for as long as six weeks. It appears unnecessary to give ampicillin when the stomach is empty. As much as 6 gm. daily has been given intramuscularly or intravenously. On conjoint administration

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*The six parts of this paper were presented, in part, at the Symposium on Antibacterial Agents sponsored by the Southern California Society of Hospital Pharmacists, Los Angeles, California, May 2, 1965.

*See Parts I, II, Minnesota Med 49:835 and 49:997, 1966.

**Mayo Clinic and Mayo Foundation: Section of Medicine.

of probenecid, serum levels of ampicillin are higher and better sustained.

Untoward Effects

Like other semisynthetic penicillins, ampicillin is cross-allergenic with the natural penicillins.

Aside from superinfection, untoward effects occur in about 5% of patients receiving ampicillin, but in only about 1% are these sufficiently severe to require cessation of therapy. Gastrointestinal irritation, including diarrhea, may occur after ampicillin is taken orally, and some patients complain of an unpleasant tasting eructation. As is well known, the penicillins can cause various skin reactions, glossitis, angioneurotic edema, eosinophilia, drug fever, anaphylaxis, and so forth. During ampicillin therapy, the serum glutamic oxaloacetic transaminase activity may be increased. In about 5% of patients, superinfection due to such organisms as *Klebsiella-Aerobacter, Pseudomonas,* and *Candida* have occurred; staphylococcal superinfection is theoretically possible.

The Cephalosporins

Cephalosporin C is an antibiotic elaborated by the fungus, *Cephalosporium.* By chemical removal and replacement of the aminoadipic acid side chain of cephalosporin C, semisynthetic compounds have been produced. The core of the cephalosporin molecule is 7-aminocephalosporanic acid. Of these partially synthesized cephalosporins, cephalothin (Keflin)[1] is commercially available, cephaloridine is currently under investigation, and cephaloglycin has given preliminary evidence of potential value. Cephalothin, cephaloridine and cephaloglycin appear to be only the initial drugs in a series which ultimately may rival the semisynthetic penicillins in numbers and variations.

Strains of *E. coli, P. mirabilis,* and *Salmonella* and *Shigella* organisms are usually sensitive to the cephalosporins, while *Klebsiella-Aerobacter* organisms and indole-positive *Proteus* ones may be insensitive. *Pseudomonas* and *Bacteroides* organisms are resistant. In general, gram-positive cocci are more sensitive to the cephalosporins than are gram-negative bacilli. Staphylococci, including penicillin G-resistant strains, pneumococci, and *Streptococcus pyogenes* and *S. viridans* are susceptible to the cephalosporins, but enterococci are often resistant.

Cephalothin and cephaloridine must be given parenterally and may be bactericidal against susceptible organisms. Cephalothin and cephaloridine are usually given in amounts of 0.5 to 1 gm. every four to six hours intramuscularly or intravenously. Cephalothin has been given intramuscularly for more than eight weeks, and 12 to 24 gm. has been administered intravenously for as long as two weeks. Cephaloridine has been given in amounts of 18 gm. for as long as a month. After reconstitution with diluent, cephalothin should be stored in the refrigerator and should not be used after 48 hours.

Untoward Effects

Untoward effects of cephalothin include thrombophlebitis when the drug is given intravenously for longer than two to three days, pain at the site of intramuscular injection, rash, fever, serum sickness, anaphylactoid reaction, transient neutropenia, eosinophilia, increased serum glutamic oxaloacetic transaminase activity, and increased azotemia. Untoward effects of cephaloridine include rash, fever, transient neutropenia, increased serum glutamic oxaloacetic transaminase, mild prolongation of prothrombin time, and probable nephrotoxicity. Superinfection from *Bacteroides, Klebsiella-Aerobacter,* or *Pseudomonas* organisms is possible with either cephalothin or cephaloridine. Cross-allergy between the cephalosporins and the penicillins has not been entirely excluded to date.

The cephalosporins, while resistant to penicillinase, may be degraded by cephalosporinase produced by certain bacteria, including strains of staphylococci and of bacilli found in the intestinal tract. If cephalosporinase-producing organisms constitute a future clinical problem, there is the possibility of synthesizing cephalosporinase-resistant cephalosporins.[2]

In the Management of Infections

It is difficult to evaluate precisely the position of cephalothin in the management of infections due to gram-negative bacilli currently, in part because of an apparent dichotomy between in-vitro susceptibilities and clinical results. That is to say, laboratory data would indicate that the drug is applicable in certain of these infections, and yet clinical response is delayed, incomplete, or occasionally absent. However, bacteremia due to bacilli originating in the intestinal tract, including *P. mirabilis* and *Klebsiella-Aerobacter* organisms, has responded to cephalothin. But, in coccal infections, cephalothin appears to be more established as an effective agent. Staphylococcal bacteremia, pneumonia, and osteomyelitis have responded to cephalothin. Pneumococcal pneumonia also is susceptible to the drug, and cephalothin may have special use in patients allergic to penicillin. Subacute bacterial endocarditis due to *S. viridans* has been managed successfully with cephalothin.

Cephaloridine[3,4] may be more potent than cephalothin against some gram-positive cocci, but conversely, cephaloridine may be less bactericidal than cephalothin against certain staphylococci and streptococci. The comparative activity of cephaloridine may be increased against strains of *E. coli,* but some studies have shown variable degrees of activity against *E. coli* and other Enterbacteriaceae. Sensitivity of *Klebsiella-Aerobacter* organisms to cephaloridine is found in less than 50% of strains. Strains of *Proteus* other than *P. mirabilis* may be no more sensitive to cephaloridine than they are to cephalothin. Cephaloridine may be active against *Salmonella* and *Shigella* but is inactive against *Bacteroides* and *Pseudomonas* organisms. As is true of cephalothin, not all strains of *Haemophilus influenzae* are sensitive to cephaloridine.

Cephaloridine is an "internal salt"; as a betaine it does not require either sodium or potassium to form a salt. In patients in whom the administration of sodium or potassium might be hazardous, cephaloridine would have an advantage over cephalothin. Also, cephaloridine may be less irritating to tissues; blood levels with cephaloridine at least equal those with cephalothin, but the duration of cephaloridine levels is considerably longer. From 30 to 40% of cephalothin is bound to serum proteins, but cephaloridine is unbound. The solubility of cephaloridine is greater than that of cephalothin, thus reducing the volume of diluent required for intramuscular injection.

Cephaloridine has been effective in serious staphylococcal infections, in bacteremia due to *E. coli,* and in pneumococcal bacteremia and meningitis. Given conjointly with streptomycin, the drug may be effective in endocarditis due to streptococcus mitis. However, some infections due to organisms that were sensitive on in-vitro testing have persisted despite treatment. Also in some patients drug-resistant mutants of the pathogen have appeared to emerge during treatment.

Since the paradox of in-vitro bacterial susceptibility and clinical ineffectiveness is shared to some degree by both cephalothin and cephaloridine, it has been proposed that the lesser pain on intramuscular injection of cephaloridine, the smaller volume of diluent required by cephaloridine, the more sustained levels of cephaloridine with less frequent injections, the fact that cephaloridine does not require sodium or potassium to form a salt, might make cephloridine more acceptable as a parenteral antibiotic than cephalothin. However, this proposal has not as yet been substantiated by clinical investigation. One potential objection to cephaloridine is that in preliminary clinical studies it was necessary to discontinue use of the drug in more than 10% of patients because of toxic reactions.

Cephaloglycin differs from cephalothin and cephaloridine in that it is absorbed after oral administration. In experimental animals the intestinal absorption of cephaloglycin appears to compare favorably with penicillin V.

Spectinomycin

Spectinomycin (Trobicin),[5,6] formerly called actinospectocin, is currently being investigated. The drug is active against strains of *E. coli, Klebsiella-Aerobacter, Proteus,* and *Salmonella* organisms. In addition, spectinomycin is active against strains of

Continued

staphylococci, streptococci (including enterococci), pneumococci, and organisms of *Neisseria.*

The drug is not well absorbed after oral administration and is given intramuscularly, usually in amounts of 0.5 gm. four times daily. In men having acute gonorrheal arthritis, a single injection of 2 gm. has been given, and results are reported to compare favorably with those of penicillin. Intramuscular injection of spectinomycin probably produces no more local pain than penicillin or chloramphenicol.

The Sulfonamides

Certain sulfonamides and allied preparations are used in specific conditions such as leprosy, ocular infections, and chronic ulcerative colitis. Aside from these preparations, the sulfonamides have use in: (1) selected infections of the urinary tract; (2) nocardiosis without involvement of the central nervous system (conjoint cycloserine-sulfonamide therapy may give an enhanced antinocardial effect), and South American blastomycosis (but in infections due to resistant strains, amphotericin B is preferred); (3) meningitis of meningococcal etiology, wherein either a sulfonamide or a penicillin has been used, and that due to pneumococci in which conjoint sulfonamide-penicillin therapy may be preferable (but today bacterial resistance should be excluded before a sulfonamide is employed as a single drug in meningococcal infections); (4) toxoplasmosis in which sulfadiazine is used conjointly with pyrimethamine (Daraprim); (5) shigellosis (but in areas where resistant strains are frequent, antibiotics such as a tetracycline or ampicillin are preferred); (6) certain infections due to members of the tribe Mimeae (but in those due to resistant strains, other therapy such as a tetracycline combined with kanamycin, polymyxin B, or colistin may be preferred); (7) lymphopathia venereum and chancroid (since sulfonamide therapy, unlike use of tetracycline, does not mask conjoint syphilis); (8) mild infections due to *H. influenzae* (but, in serious infections, other regimens, like streptomycin-tetracycline, chloramphenicol or ampicillin have been preferred); (9) glanders, and (10) prophylactically against recurrences of rheumatic fever in persons allergic to penicillin. In the past, 2 gm. of sulfadiazine were given for two to three days to carriers of meningococci, but currently, even when resistant strains are excluded, there is doubt about the efficacy of the regimen unless its duration is considerably increased.

Clinical Application

Of the multiple sulfonamide preparations commercially available, the following, grouped according to their usual clinical application, are representative: (1) those used for systemic effect, including sulfadiazine, sulfamerazine, and sulfamethazine, which are known collectively as the sulfapyrimidines and are sometimes employed in combination in attempts to lessen the likelihood of renal toxicity; (2) those used in urinary infections, including the short-acting drugs such as sulfisoxazole (Gantrisin), sulfisomidine (Elkosin), and sulfamethizole (Thiosulfil), which sometimes are also employed for systemic effect, and in addition the long-acting drugs exemplified by acetyl sulfamethoxypyridazine (Kynex), sulfaethidole (Sul-Spansion), and sulfadimethoxine (Madribon); and (3) those used for intestinal antisepsis including sulfaguanidine, phthalylsulfathiazole (Sulfathalidine), and succinylsulfathiazole (Sulfasuxidine), which are poorly absorbed on oral administration and hence have special enteric application.

Untoward Effects

Although the sulfonamides in current use are less toxic than those employed previously, on rare occasions they cause such untoward effects as drug fever, dermatitis, nephrotoxicity, blood dyscrasias, and allergic vasculitis. Cyanosis, anaphylaxis, hepatitis, peripheral neuritis, conjunctivitis, and serum sickness are uncommon today. Nausea, vomiting, photosensitivity, dizziness, and headache occur occasionally. Mental disturbances have occurred on use of the sulfapyrimidines. Administration of a sulfonamide to a woman near term may produce kernicterus in the fetus. Nephrotoxicity may reflect either precipitation of the acetylated derivative in the tubules or hypersensitivity; hypersensitivity may affect the kidney directly, producing a nephritic or nephrotic syndrome, or the reaction may be indirect via an angiitis of the kidney and other organs. Alkalinization of the urine may decrease crystallization, but it also increases the rate of drug excretion and lowers the blood concentration, requiring increased administration to produce bacteriostasis. Sulfisoxazole (Gantrisin) and sulfisomidine (Elkosin) are more soluble in urine of variable pH than are sulfadiazine and sulfamerazine. Special care may be required with sulfamethoxazole (Gantanol) to avoid crystalluria because of the high degree of acetylation of the drug in the urine. Cross-hypersensitivity to various sulfonamides is common.

Use of the sulfonamides may unmask or precipitate clinical manifestations of previously inactive processes in certain predisposed individuals. In patients having erythrocytes deficient in glucose-6-phosphate dehydrogenase, hemolytic anemia may occur, and in those having porphyria or lupus erythematosus, acute manifestations may be precipitated.

Because use of the long-acting sulfonamides appears to have resulted in development of Stevens-Johnson syndrome (erythema multiforme exudativum), it is advised that one first consider administration of a short-acting sulfonamide. Because it may take several days for the long-acting sulfonamides to be metabolized and excreted, it is thought this characteristic may contribute to the severity of adverse reactions in susceptible individuals. Over 100 cases of the complication have been reported to date and two thirds of the patients were children. This complication has had a mortality rate of about 25%.

Dosage and Route of Administration

Sulfonamides for systemic effect are given in a maximal oral dose of 4 to 6 gm/day, sometimes following an initial dose of 4 gm. In systemic infections, a blood concentration of sulfonamide of 10 to 15 mg/100 ml. is recommended.

In management of urinary infections, the short-acting sulfonamides are given in amounts of 0.5 to 1 gm. four times daily, whereas 0.5 to 2 gm. of the long-acting derivatives are administered once or twice daily. When the poorly absorbed sulfonamides are given to produce intestinal antisepsis, as much as 8 gm. daily is administered in divided doses.

The sodium salts of these drugs, such as sodium sulfadiazine and sodium sulfisoxazole, are given intravenously. Via this route, the usual initial dose is 3 to 4 gm., with 1 to 2 gm. being given every eight to 12 hours thereafter.

The Nitrofurans

Nitrofurantoin (Furadantin) is effective in the majority of acute uncomplicated infections of the urinary tract due to *E. coli*. The drug may also be useful in streptococcal and staphylococcal infections of the urinary tract but is less likely to be effective in those due to *Klebsiella-Aerobacter, Proteus,* and *Pseudomonas* organisms. The emergence of bacterial strains resistant to the drug has not been a problem.

The oral dose of nitrofurantoin is 50 to 100 mg. four times daily. There is a preparation for intravenous administration, but justifiable indications for its use are rare.

Untoward effects include nausea, vomiting, fever, and rashes. Transient alopecia, pleuropneumonitis, asthma, anaphylactoid reactions, jaundice, and polyneuropathy are less frequent. As with the use of fava beans, acetanilid, sulfonamides, and primaquine, patients having erythrocytes deficient in glucose-6-phosphate dehydrogenase may develop hemolytic anemia during therapy with nitrofurantoin.

A nitrofuran presently being investigated in the management of urinary infections is NF 246. The drug appears to be effective against *E. coli* organisms and streptococci, including enterococci, as well as against strains of *Proteus* organisms. It may be effective against *Klebsiella-Aerobacter* and *Salmonella* organisms, but appears to be ineffective against strains of *Pseudomonas*.

Continued

Furazolidone (Furoxone) is designed for oral use in cases of bacterial enteritis. Strains of *E. coli, Proteus, Salmonella,* and *Shigella* organisms as well as streptococci and staphylococci are said to be sensitive to the drug. A 100-mg. dose four times daily is recommended. Nausea, vomiting, headache, hemolytic anemia, and, after ingestion of alcohol, a disulfiramlike effect may occur.

Nitrofurazone (Furacin) is used in various forms, including powder, ointment, creams, suppositories, and solutions, in the management of surface infections. Preparations are available for the management of skin lesions, vaginitis, trigonitis and for optic, otic, and nasal instillation. Sensitization appears to be uncommon.

Furazolidone and nifuroxime (Tricofuron) are used in combination in suppository and powder forms for vaginitis due to *H. vaginalis, Trichomonas,* or *Candida.* Furazolidone is antibacterial and trichomonacidal, whereas nifuroxime is fungicidal.

Nalidixic Acid

Nalidixic acid (Neg-Gram), a naphthyridine derivative, is used as a urinary antiseptic and is active against strains of *E. coli, Klebsiella-Aerobacter,* and *Proteus* organisms but is usually ineffective against *Pseudomonas, Salmonella, Shigella,* and coccal organisms. Preferably, in-vitro bacterial susceptibility studies should be carried out before nalidixic acid is used.

A 0.5 to 1-gm. dose of the drug is given orally four times daily. After two weeks of therapy, it is recommended that the daily dose not exceed 2 gm. An intravenous preparation is being investigated.

Untoward effects include gastrointestinal irritation, rashes, fever, headache, photosensitivity, visual disturbances, stimulation of the nervous system and, conversely, somnolence. Possible cases of bleeding from the gastrointestinal tract have occurred, and it is suggested that nalidixic acid may decrease ventilation in patients with respiratory deficit. Eosinophilia, leukopenia, increased serum glutamic oxaloacetic transaminase activity, increased azotemia, and possible hepatotoxicity have been noted. Resistant bacterial strains may emerge during therapy. False-positive tests for urinary glucose, and possibly true glycosuria, may occur. Nalidixic acid may have an antipyretic action similar to aspirin.

The Methenamines

Methenamine mandelate, a salt of equimolecular quantities of methenamine and mandelic acid, is used in acute uncomplicated infections of the urinary tract. The mandelic acid component of methenamine mandelate helps acidify the urine, releasing formaldehyde from methenamine. The formaldehyde is antibacterial to both gram-negative and gram-positive organisms, but the drug has use mainly in enterococcal infections. Despite the mandelic acid component, supplemental acidification may be required, particularly with urea-splitting organisms.

A dose of 0.5 to 2 gm. of the drug is given orally three or four times daily.

Untoward effects include nausea, vomiting, diarrhea, and skin rashes. Dysuria and albuminuria are uncommon, and hematuria is rare.

Methenamine hippurate is a compound in which mandelic acid is replaced by hippuric acid; but currently the compound is available only for investigational use.

The Acidifying Agents

The acidifying agents include such drugs as methionine, ammonium chloride, ammonium mandelate, calcium mandelate, and ascorbic acid. However, in recent years, use of methionine has been emphasized.

Decrease of urinary pH and bacterial counts may follow use of 8 to 15 gm. of methionine daily. However, when more than 8 gm. of the agent is given per day, the patient may note the odor of hydrogen sulfide about his person. The sulfur in methionine is oxidized to sulfate and is excreted in the urine, making it acidic. To minimize the patient's complaints regarding the odor-producing effects of methionine, some workers avoid the use of higher drug doses by conjoint administration of other acidifying agents like ammonium chloride. If the urinary pH can be reduced to 5 or less by conjoint use of these agents, the desired antibacterial effect may be procured, but it is difficult to maintain such a pH without inducing metabolic acidosis. With the availability of other effective drugs such as the sulfonamides, nitrofurantoin, and nalidixic acid, such cumbersome regimens as are required in attempts at acidification have rare application today.

Use of an acid-ash diet or large quantities of cranberry juice (which contains quinolic acid) in attempts to render the urine acidic are also not in common use currently.

When attempts are made to keep the urine acidic, the patient is advised regarding restriction of his fluid intake to 1,200 ml. a day and the avoidance of foods (primarily citrus fruits) and drugs (such as sodium bicarbonate and milk of magnesia) which increase the alkalinity of the urine. Also, the patient should periodically determine, by means of nitrazine test paper, whether his urine is properly acidic.

In this regard, adjustment of urinary pH has been said to enhance the activity of certain drugs in addition to methenamine mandelate in the management of urinary infection.[7] Antibacterial activity of the tetracyclines, novobiocin, and cycloserine may also be augmented at acid pH, whereas penicillin, erythromycin, streptomycin, neomycin, kanamycin, and gentamicin may be more potent at an alkaline pH. It is said that results with sulfonamides and chloramphenicol vary with the organisms tested and that the action of nitrofurantoin may not be greatly influenced by adjustments of pH. However, the majority of clinicians ordinarily do not place great emphasis on adjustments of urinary pH by employment of these additional drugs.

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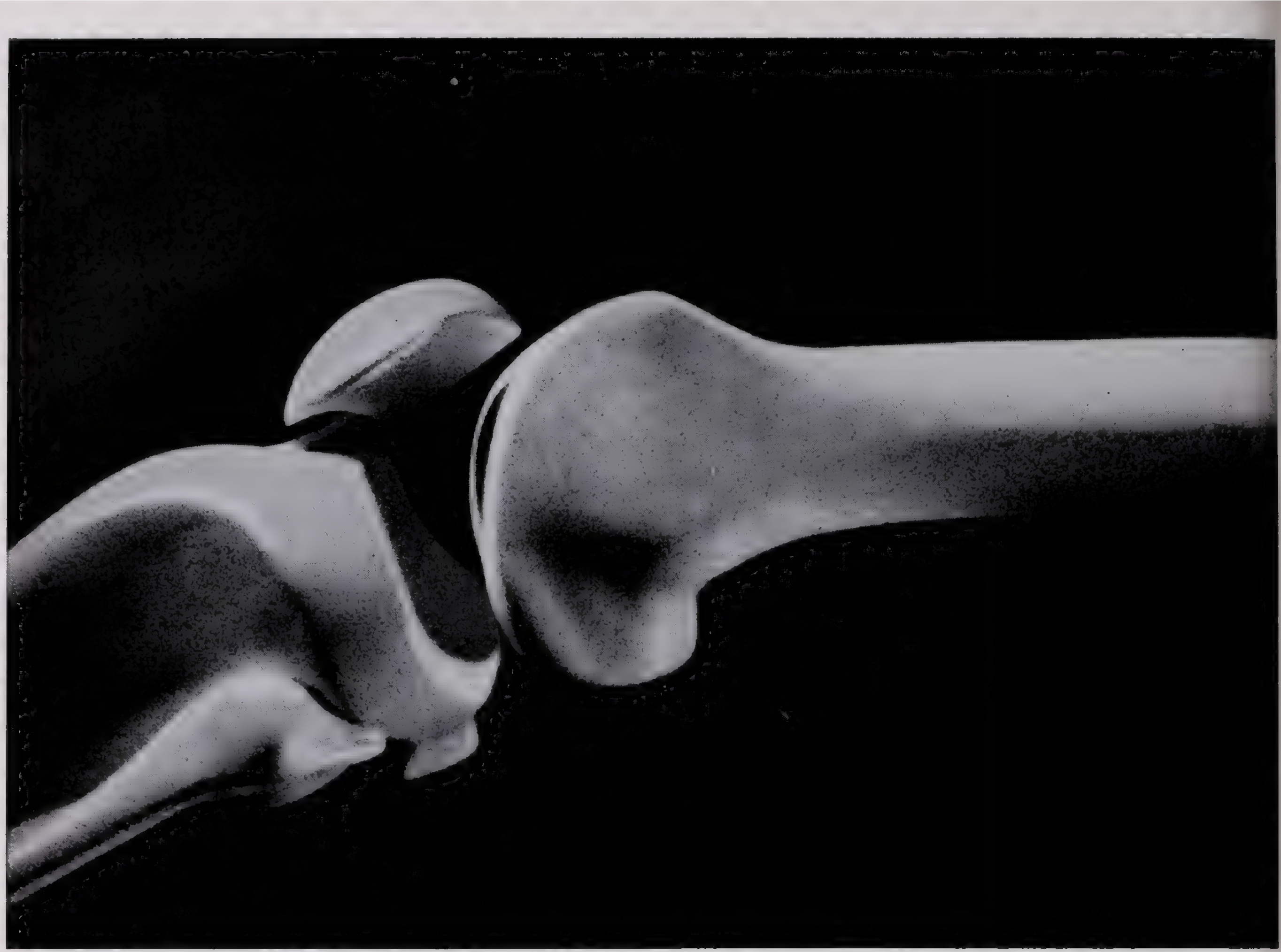
Your Age

In China, the 51st birthday is an occasion of great rejoicing, the 61st and 71st are progressively happier and grander; while a man able to celebrate his 81st birthday is looked upon as one specially favored by the gods.
— Lin Yutang

On Being a Patient

You cannot be a perfect doctor, till you have been a patient. You cannot be a perfect surgeon, till you have enjoyed in your own person some surgical experience. Enjoyed, I say, and stick to the word. Count the ways of enjoyment. To be the dear object of so much care and friendship, to be compassed about with hopes and prayers, is there no pleasure in that? To behave nicely, and nothing common do or mean, upon that memorable scene, but lie on the operating-table like Patience on a monument, is there no pleasure in that act of self-control? — Stephen Paget (1855-1926)



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Precautions
Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patient should be closely supervised and should be warned to report immediately fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools. Make regular blood counts. Use greater care in the elderly.

Warning
If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy.

Adverse Reactions
The most common are nausea, edema and drug rash. Hemodilution may cause moderate fall in red cell count. The drug may reactivate a latent peptic ulcer. Infrequently, agranulocytosis, generalized allergic reaction, stomatitis, salivary gland enlargement, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported but cannot definitely be attributed to the drug. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hepatitis, jaundice, and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently.

Dosage
The initial daily dosage in adults is 300-600 mg. daily in divided doses. In most instances, 400 mg. daily is sufficient. When improvement occurs, dosage should be decreased to the minimum effective level: this should not exceed 400 mg. daily, and is often achieved with only 100-200 mg. daily.

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Medical Ethics

Can the Best be Better?

Address by Walter H. Judd, M.D.
First National Congress on Medical Ethics
Chicago, Illinois
March 5, 1966

The pursuit of excellence is a part of the spirit and tradition of America, and particularly of our profession. We instinctively feel that the best can always be made better.

Physicians are expected to assume this fact, but is it in keeping with the "honor and dignity" of the profession to make a public point of it and to make comparisons which might seem to reflect unfavorably on other professions?

To take stock of ourselves is why we are gathered in this First National Congress on Medical Ethics. We have been so preoccupied with our shortcomings — both those that are real and those not real but attributed to us in much of the public mind — that the picture can be seen in perspective only if we consider, at the outset, the bright and positive side also.

No less an authority than our distinguished morning speaker, Professor Everett Hughes, Ph.D., alluded to medicine as "the queen of the professions." The National Opinion Research Center, rating some 90 occupations, stated that the physician was rated most desirable of all except Justice of the United States Supreme Court. Diplomats, chemists and lawyers were tied for tenth place. Dentists, architects and county judges were tied for the fourteenth with psychologists and ministers tied for seventeenth. To the extent that other professions and the public as a whole rate the profession of medicine as the "best," why should this be so?

The ten Principles of Medical Ethics provide, I believe, the basic reasons. They are the blueprint and the foundation stones on which Medicine's house has been built. Both the principles and the accomplishments of the profession can be broken down into three categories: (1) the science of medicine; (2) the socioeconomics of medicine; and (3) the art of medicine.

The Science of Medicine

It is a well established ethical concept that every physician should aid in safeguarding the public and the profession against admission to it of those who are deficient in moral character, education, or professional competence.

In 1905, 28 per cent of all college graduates were entering the field of medicine. This situation prompted President Gilman of Johns Hopkins to remark that the medical student was likely to be "one son of the family too weak to labor on the farm, too stupid for the bar and too immoral for the pulpit." Only five medical schools required as much as two years of college as a prerequisite for matriculation. Today the Admission Committees of our 88 schools require at least three years, and almost all strongly recommend the completion of four years of college or its equivalent.

It is a fact that the cream of our youth has been attracted to the medical profession and the problem is not so much one of screening out undesirables as it is of making wise decisions in selecting from those who are already the "best," the ones who have the best character, best minds, best aptitudes, best motivation.

Continued

In order to make certain that there is no insurmountable economic barrier to admissions, the medical profession has supported scholarships and loan funds. Notably, the AMA in 1962 launched its medical education loan guarantee program which now has made 27,000 loans totaling more than $32 million to medical students, interns and residents.

The medical profession has taken the lead in securing the enactment in the states of Medical Practice Acts and Basic Science Acts and in supporting the state boards which administer them. It has established a National Board of Medical Examiners to prepare and administer qualifying examinations of high quality. It has also established the Educational Council for Foreign Medical Graduates to verify the credentials, evaluate the educational qualifications of foreign-trained physicians, and assist those who desire to advance their education in the United States.

The medical profession has recognized for years that instruction in medical school is only a prelude to a lifetime of striving for ever greater competence in the care of the sick. Thirty-seven of our fifty states require the completion of approved internship, and there is a yearly increase in residency training in the several specialties. The profession, again acting through its own agencies, has established the basic criteria for approval of internships and residencies, and on-site surveys are conducted to be sure the standards are met.

Although the "policing" actions by hospital medical staffs are well known to you, and Doctor Appel described them this morning, I venture to say that the public generally is unappreciative, because unaware, of the manner in which physicians voluntarily, as members of a hospital staff, impose requirements on themselves to insure a high quality of medical service. It is not the government; it is the medical staff that has always been and is the guardian of the high quality of medical service rendered in our hospitals. And when has any profession ever worked so hard to reduce its own income by eliminating or reducing the incidence of the diseases and suffering which it is the physician's livelihood to treat?

The Socioeconomics of Medicine

The profession was *not* prepared, either by tradition or training, for the explosion in the socioeconomic fabric of our society. The physician was accustomed to intimate doctor-patient relationship without the intervention of any third party. Three decades ago problems concerning the distribution of medical services were comparatively minimal. Today they are monumental. Notwithstanding these considerations — and despite the abuse that has oftentimes been directed at the medical profession because it did not embrace various schemes proposed for the intervention of third parties in the doctor-patient relationship — there is much accomplishment in this area.

Prepayment Plans

The profession has aided in the development of voluntary health insurance and prepayment plans as the best mechanism for paying for medical and hospital care. It has developed guides for evaluating medical care programs for those financially unable to pay their way. It has supported and cooperated with numerous programs at all levels of government designed to provide medical services to those who would not otherwise be able to obtain them. It has aided governmental programs for veterans, military personnel and their dependents and federal employees. Currently, it is studying various proposals for postpayment of medical bills to determine whether, operating under suitable safeguards, they too may reduce economic barriers to maximum health care.

Physicians' Fees

It has generally maintained physicians' charges at fair and reasonable levels. According to the 1964 Report of the Commission on the Cost of Medical Care, physicians' fees had risen only 112 per cent since 1935 as compared with 123 per cent in the over-all cost of living, 136 per cent in the total cost of medical care, and 480 per cent in hospital daily service charges.

The physician continues to observe the ethical guidelines that "his fees should be commensurate with the services rendered and the patient's ability to pay" and that "poverty of a patient * * * should command the gratuitous services of a physician." On the average, today's physician spends about one eighth of his time in providing free care. In 1960 physicians donated approximately $658 million in free medical care.

The physician insists that no payment plan interfere with or impair the free and full exercise of his medical judgment and skill or tend to cause a deterioration in the quality of medical care.

The Art of Medicine

May I group under "The Art of Medicine," those Principles of Medical Ethics which emphasize personal care of the patient and relationships between physicians.

These ethical guidelines may be summarized as follows: "The principal objective of the medical profession is to render service to humanity; reward or financial gain is a subordinate consideration. Fees should be fair. Unnecessary services or unnecessary facilities should not be provided or prescribed. Confidential communications between physician and patient should be respected. There should be mutual free choice between physicians and patients in entering into the doctor-patient relationship. A patient should be neither neglected nor abandoned. The physician should neither exaggerate nor minimize the gravity of a patient's condition. One physician should do nothing to diminish the trust reposed by a patient in his own physician. Physicians should uphold the honor and dignity of the medical profession and expose 'without hesitation, illegal or unethical conduct of fellow members of the profession.' Physicians should not solicit patients. 'There is but one code of ethics for all, be they group, clinic or individual and be they great and prominent or small and unknown.' "

There is, of course, no accurate yardstick by which the degree of compliance with these Principles may be measured, particularly those dealing with the physician's personal attention to his patient and his relation with his fellow-physicians. I am of the opinion that some of these principles are more wholeheartedly honored and observed by the profession today than ever before. Present public opinion obviously believes some are less well observed today than in former years. Undoubtedly this opinion is influenced by a nostalgia which magnifies the virtues of the past and also the shortcomings of the present as reflected in the isolated cases which come to public attention.

Yet we know that in our profession — as in others — there does exist a minority who must be controlled or disciplined if the moral tone of the profession is to be maintained at the highest level. This is the negative approach to medical ethics, but it is necessary and must be pursued courageously. That the medical profession is well aware of this fact is evidenced in part by the creation by the AMA Board of Trustees of a Medical Disciplinary Committee.

Disciplinary actions reported by state boards of medical examiners and state medical societies are, of course, only the visible part of the iceberg and give no indication of the volume of formal or informal grievance and disciplinary proceedings that occur each year. Most complaints against physicians are and should be handled by the physician himself in consultation with the complaining patient. When this does not bring satisfaction, or when the patient does not take his grievance directly to his physician, complaints are made to county and state medical societies and occasionally to the AMA, which invariably refers them back to the county medical society for attention. It is at this important level that all but a few of the more serious cases are handled, grievances resolved, and discipline imposed — usually without publicity.

Because medical society membership is so valuable and therefore coveted, the only sanction available to medical societies — that of expulsion or suspension from membership — is highly effective in most instances. In those cases in which the offender is not a member of a medical society, it may

Continued

be necessary to resort to sanctions authorized by state law.

While the record of the medical profession in the field of ethics and discipline justifies our feeling that it is the "best," we need to consider now some areas in which greater progress and improvement should be made. Even though ten new medical schools have been created since World War II and an additional fourteen are in process of being organized, the medical profession has a continuing obligation to take the lead in making certain there is always an adequate supply of properly-trained physicians to meet the needs of the public, both present and projected.

In the field of socioeconomics, it is obvious that the profession should try even more aggressively to propose and promote ways and means of meeting any public need for better distribution of medical services — always within the Principles of Medical Ethics.

Expectation of reward and financial return in accordance with one's merit and effort are powerful incentives to a physician, as to anyone else, to broaden his skills, improve his service, do his utmost for his patient. It is the public that has most to gain from provision of such incentives. They do not cheapen medical practice; they can elevate and enhance it. Unless medicine can remain attractive financially it will not attract the quality of students it must have if it is to be able to do what the public needs and wants from it. "In the practice of medicine a physician should limit the source of his professional income to medical services actually rendered by him, or under his supervision, to his patients."

Under this principle come those vexatious problems of physician-dispensing of drugs, eye glasses, etc., physician-ownership of pharmacies and drug repackaging companies, and the problem of fee splitting. It is in this sensitive area, particularly, that substance is more important than form — that the spirit must go beyond the letter. The medical profession has been challenged by legislation already enacted and the threat of additional legislation concerning the ownership of pharmacies and the dispensing of glasses. Although many of these attacks may be motivated more by economic than by ethical considerations, they cannot be ignored.

Obviously grievance and disciplinary mechanisms are valueless if they are not used. And clearly, there is room for improvement at this point. In general, "men of good conscience inherently know what is right and wrong, and what is to be done or to be avoided." But it does not follow that all ethical questions are so clear that men of good conscience will invariably agree on the proper answer. This Congress has been brought together in order that physicians, known for their exemplary integrity and public spiritedness may reason together, exchange experiences and viewpoints and find inspiration and motivation to rededicate a great profession at the peak of its powers to its finest traditions and its finest ideals. It is not enough just to refrain from behaving unethically. The profession needs a new pride, a new enthusiasm for excellence in the high duties entrusted to it that will make every physician *want* to behave *ethically* in the highest sense of the word, to go beyond the things required by rules or regulations — for the sheer satisfaction and joy of it. One cannot fail to see a serious challenge to the profession's freedom in the activities we witness in various quarters designed to persuade the people that their trust and confidence in medical matters would be better placed in government than in the medical profession. Unless the profession can *win* this competition for the primary confidence of the people, and maintain and strengthen the people's trust, it runs the grave risk of being converted into a public utility subject to the sort of regulations that are imposed on power and transportation.

The medical profession has enemies that it would be a mistake to regard as men of good will. On the other hand, not all of our critics have sinister or selfish motives. Some are within our own ranks and are seeking to stimulate the medical profession to rededicate itself to those principles which have made it peerless. Medicine is not alone in this struggle. Lawyers, ministers, dentists, engineers, architects and many others have more in common with us than they or we have yet realized in preserving professionalism as a most important part of American life. All professionals and the public alike must be constantly reminded of the important distinctions between a profession and a business, a trade or a union. It is essential for America's greatest future that a worthy medical profession remain free and strong, free practitioners of a high calling, not government-directed technicians. The key to this result is to merit and to command public trust and confidence. This does not come in the bargain basement. It must be deserved and it must be striven for. Its price, like that of liberty, is eternal vigilance. The key is in your hands. Take it home and unlock the doors to the future. May my last paragraph be the substance of the last paragraph of our oath. The wisdom of the immortal Hippocrates 2,300 years ago is relevant today:

"With our oath unviolated it will be granted to us to enjoy life and the practice of the art respected by all men at all times."

Tar Water

One of the most amusing incidents in the history of drugs is that of Bishop Berkeley's tar water. This precious fluid was made by stirring a gallon of water with a quart of tar and letting it stand forty-eight hours and pouring off the clear water. Absolutely nothing of any chemical significance had been dissolved out of the tar by the water but the smell of the tar clung to the fluid and so it was rather easy to persuade one's self that one must be taking something. Modern physicians use it occasionally for diluting lotions which are meant to prevent itching. Bishop Berkeley, however, found it a cure for everything. Yes, quite literally everything.

According to his own list it cured "gout and fevers, coughs, pleurisy, peripneumony, erysipelas, asthma, whether it came from the heart or the kidneys, indigestion, hysterics, mortification, scurvy, cachexia — which in that period usually meant cancer — hypochondria, liver disease, and dropsy," and was besides an excellent preservative for the teeth and gums. Too much of it could not be taken, it must be taken for at least a month before much effect could be expected of it and sometimes two or three months were necessary to bring about the beginning of relief from it.

Berkeley is the great idealist philosopher, one of the greatest thinkers perhaps in English philosophy, but he held two very odd opinions: namely, "that tar water was everything and that the whole material universe was nothing." Tar water is still with us, but that very fact only demonstrates beyond all doubt what a fool dear Bishop Berkeley made of himself over it.*

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*Walsh, James J., M.D., Ph.D., Sc.D.: Cures, D. Appleton & Co., 1924.

Rhubarb

Rhubarb has manifestly in it parts of contrary operations; parts that purge and parts that bind the body; and the first lie looser and the latter deeper, so that if you infuse rhubarb for an hour, and crush it well, it will purge better and bind the body less after the purging than if it stood twenty-four hours. — Lord Bacon

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Getting education is like getting measles; you have to go where measles is.

— Abraham Flexner

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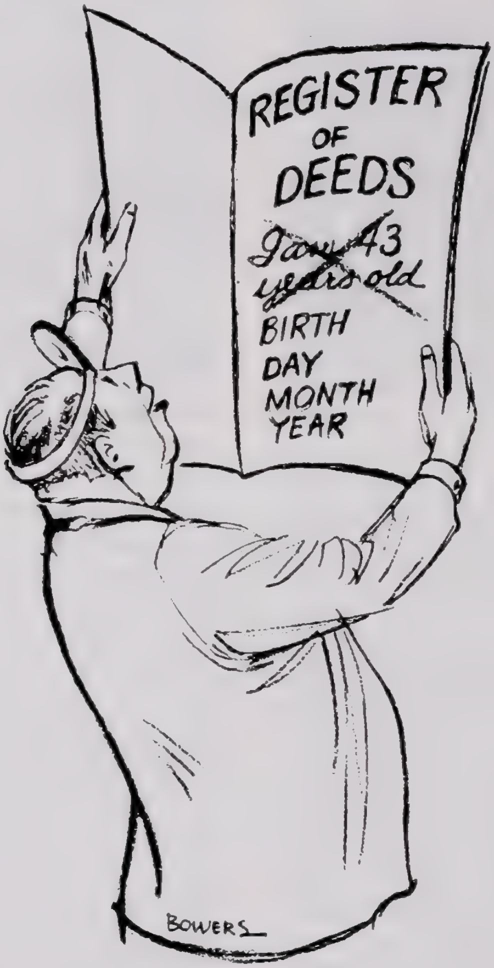

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Abstracts, Briefs and Commentaries

A PENETRATING WOUND OF THE ABDOMINAL AORTA

In a survey of penetrating wounds of the heart and aorta, those of the aorta prove to be the most dangerous. Of patients with aortic lesions only one in five lives long enough to get to the hospital; yet the mortality rate is only 30 per cent. Statistics indicate that 14 out of 100 patients with aortic wounds survive. At the Helsinki Hospital one man with this 14-per-cent chance survived.

Case Report

A mechanic, aged 17, drunk at the time, was stabbed twice. Ten minutes later he arrived at the hospital, with no first aid given en route. On arrival the patient was pale and shocked. The radial pulse was absent and the blood pressure too low to record. In the right thoracic wall below the breast was a 15-cm. stab wound. This wound did not involve the pleural cavity or the liver. A second wound, 2 cm. long, 1 cm. to the right of the umbilicus, was also present, from which spurted arterial blood. A blood-filled loop of intestine herniated through this wound due to intra-abdominal pressure. Treatment: An infusion of Mercrodex® was started in the cubital vein, followed by transfusions of O R uncrossed blood. Additional blood was given through four portals with the patient in deep Frelenburg position, and the blood pressure rose to 40/mm.

Under general anesthesia a long paramedian incision was made. Huge distended loops of intestine filled with blood erupted together with a powerful stream of arterial blood. By pressing the aorta against the spine with both hands, bleeding was arrested and the radial pulse could be palpated. The actual bleeding point was visualized and bleeding controlled by pressure at that point. A tangential cut 1.5 cm. was located on the right side of the aorta just above the inferior mesenteric artery. Forty minutes elapsed between the patient's entrance to the hospital and the control of the bleeding.

Using blood-vessel clamps for adequate exposure the aortic laceration was sutured with 4-0 silk. Search of the intestinal tract revealed a cut through the mesocolon and the duodenal wall, through which blood entered the stomach and the small intestine to the cecum. Two 2-cm. wounds of the duodenum were sutured. Shock and hypotonia did not disturb the intestinal or renal function, however. The operating time was four and a half hours. The patient received ten and a half liters of blood. After 26 days of hospitalization he was discharged. Four months later an aortogram was negative. Three months following the massive blood transfusions the patient developed serum hepatitis from which he recovered.

Discussion

Penetrating wounds of the aorta are usually caused by gunshot or stabbing. In Beall's 1960 series the abdominal aorta was involved in 14 patients out of 23, and of 14 treated by surgery four survived. Beall reports four

Continued

additional survivals found in the literature, making a total of eight known cases that survived.

If the patient's blood group is not known, O Rh negative blood is used. It is important not to change to the patient's own group if five units or more of the O group have been given. This danger persists for about two weeks.

An extremely critical moment and danger of exsanguination of the patient occur when the abdomen is opened. Immediate firm pressure of the aorta against the spine is imperative. After a period of waiting until the blood pressure takes an upward turn, further surgical procedures may be instituted. Vascular repair follows the application of vascular clamps. Clean lacerations may be sewn, but ragged lacerations may demand a patch graft or an aortic prosthesis of teflon or dacron. If a patient, just before arrival or on arrival, suffers a cardiac standstill, steps for resuscitation and surgical treatment are suggested.

Stanley R. Maxeiner, Sr., M.D.
Minneapolis, Minnesota

Alfthau, O., Lindstrom, B. L., Makela, K., and Tarkkanen, V.: Department of Surgery, Maria Hospital, Finland. Acta Chir Scand 129:675, 1965.

ADDENDUM TO ARTERIAL INJURIES ASSOCIATED WITH FRACTURES

Makin, Howard, and Green have also reported on the necessity of a more aggressive approach when an arterial injury is a complication of a fracture or dislocation. They have shown in a study of 16 patients that when active treatment to the impaired circulation is attempted within the first 12 hours, the number of recoveries is much greater than when active therapy is delayed. Whenever arterial damage is suspected, they urgently suggest arteriography, which is to be followed immediately by operative restoration of the impaired arterial flow, because failure to restore the circulation results in permanent damage by ischemia or gangrene and eventual amputation. They make a plea suggesting that the training program for surgeons who expect to treat patients with injuries include the diagnostic and operative management of arterial injuries.

Carl O. Rice, M.D.
Minneapolis, Minnesota

Makin, G. S., Howard, John M., and Green, Robert L.: Arterial Injuries Complicating Fractures or Dislocations — The Necessity for a More Aggressive Approach. Surgery 59:203, 1966.

DIAGNOSIS OF DROWNING

Measurement of differences in plasma total solids between right and left heart blood by means of the total solids meter, a temperature-compensated hand refractometer, is shown to be at least as reliable as the measurement of osmolarity or chloride, especially as a test for fresh water drowning. This new, rapid, and simple technic has been evaluated in terms of other tests for fresh and sea water drowning, and it appears to provide a useful adjunct to present diagnostic methods.

Courtesy of References and Reviews
Journal of the American Medical Association

Chiaraviglio, E., and Wolf, A.: Arch Path 75:337, 1963.

A CAUSE FOR REPLANTATION FAILURE

Failure in limb replantation is often attributed to factors beyond the surgeon's control. Recently in the Milwaukee area a review of two attempts at preservation of a limb demonstrated that well known principles of vascular surgery may be unwittingly violated.

A few milliliters of a weak heparin solution injected through the artery wall was expected to prevent thrombosis in a limb without any circulation. Perfusing a limb for at least 15 minutes to flush out thrombi was not accomplished. The restoration of venous circulation was omitted. Cooling of tissues to prolong viability while they were without circulation was not done.

Steps were taken to insure that circumstances would favor success at the next opportunity of limb reimplantation. A team was formed to include surgeons experienced in vascular and orthopedic procedures. Several bottles of lactated Ringer's solution were stored in the operating room refrigerator with instructions for adding heparin, antibiotics and low molecular weight dextrose to make up a suitable solution for perfusing the limb by gravity flow. Instructions for management of the patient and the amputated limb were issued to rescue teams, to operating room personnel, and to emergency room personnel. Shortly after this the following incident occurred.

Report of Case

A skilled mechanic injured in a machinery explosion was brought to the Milwaukee County Hospital 30 minutes after the injury. The left hand had been severed at the distal radius level. The hand was not brought with the patient and had to be retrieved at the site of the accident.

One team of two surgeons cleaned the hand and perfused it with the prepared iced solution and placed a rod in the ulna and a plate on the radius. During evaluation of the patient's other injuries (including a depressed skull fracture) their definitive treatment was delayed. A second team debrided the arm stump. Bony fixation was accomplished without delay. Shortening of the bones permitted excision of ½ inch of each end of the radial artery before anastomosis. The artery was opened as soon as the vein anastomosis was completed, 4½ hours after surgery. The ulnar artery was sutured to a large branch on the ulnar aspect of the wrist. Nerves were identified and tagged. The wrist tendons were sutured and the skin closed.

When good appearance of the hand did not persist, a variety of supportive measures were instituted to overcome vessel spasm. Fourteen hours later the hyperbaric chamber was used for two hours at three atmospheres of pressure. Improvement of the hand was definite. In the next 36 hours five more similar treatments of 30 minutes each were given.

Sixty hours after reattachment of the hand a fluorescein test revealed no circulation and re-amputation was done.

Method of Study

The vessels were excised at the anastomoses and prepared for microscopic sections. The radial artery just below the anastomosis was hemorrhagic and revealed fragments of bone and cotton fibre imbedded in its wall, not detected at the time of surgery. X-ray examination after hypaque injection showed good filling of the deep volar arch and small vessels to the thumb and index finger. A puddle of dye in the palm of the hand was due to extravasation from the ulnar artery. Dissection showed that the distal portion of the ulnar artery was retraced into the palm and that the ulnar artery had been sutured to a branch of the palmar end of the ulnar artery. Failure was blamed on thrombosis occurring at the site of the unrecognized foreign bodies and the injury to the radial artery.

Continued

Discussion: Dr. Edward J. Beattie, Jr. of Chicago reported a similar case in which the hand was saved after being severed in a paper cutting machine. The hand was flushed with cold heparinized saline. The bones were pinned and the radial artery anastomosed. The veins presented the greatest difficulty. A thorough and careful attempt to get as much venous return as possible to avoid excessive edema of the hand is important. The hand of their patient had sufficient lymphedema to necessitate multiple pie-crust incisions. Because there was good retrograde flow of blood from the cut-off end of the ulnar artery it was not anastomosed. This may have been a good procedure as it gave less venous run-off and less edema. Because of the edema this patient did lose his little finger and fifth metacarpal.

In their case other hand structures such as nerves and tendons were not sutured. Dr. Beattie's impression is that these tissues should be sutured together at the time of the original surgery, as they found later repair was extremely difficult because of marked retraction. In their experience with this patient, the lymphatics regenerated rapidly. Experimentally in dogs they regenerate in about seven to eight days. Dr. Beattie thinks this was the first attempt at such an operation. This patient has a hand, not a perfect one, but one with a pincer-like grip, and when last seen sensation had returned to the terminal joints of the fingers.

Comment: It would seem to be no great effort to accept the recommendations drawn up by the Milwaukee Hospital committee. Where trauma care is given, a team made up of surgeons trained in the surgery of trauma and of blood vessels could be available. Cold solutions of lactated Ringer's solution with anticoagulants and antibiotics should be available for prompt perfusing. Pressure by gravity should not be exceeded. Instructions should be given to emergency room personnel, ambulance attendants, and others regarding care of the patient and of the amputated member. If organs can be successfully transplanted, perhaps extremities may also be transplanted and be more functional than a traumatized replantation.

Stanley R. Maxeiner, Sr., M.D.
Minneapolis, Minnesota

Worman, Leonard W., Darin, Joseph C., and Kritter, Alfred E., Milwaukee: The Anatomy of a Limb Replantation Failure. Arch Surg 91:2, 1965.

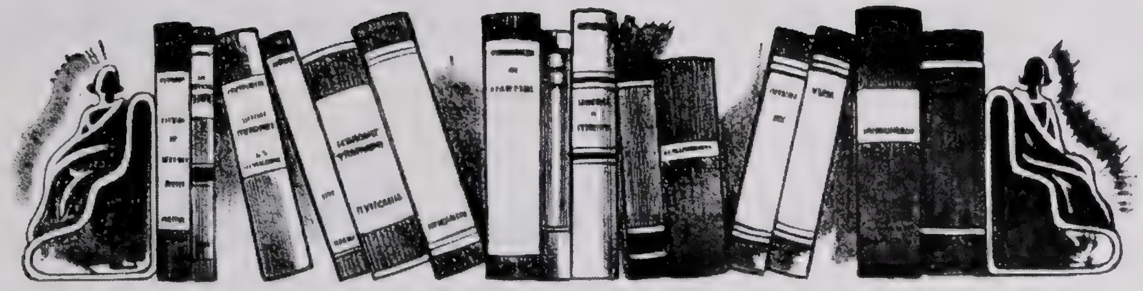
PANCREATITIS IN CHILDREN

Pancreatitis was encountered in 18 hospitalized children. The diagnosis was established clinically in four children and at postmortem examination in 14. Clinical findings, associated disease, laboratory data, and postmortem findings are described in the 14 patients who died and four who survived. Steroid administration, congenital anomalies, mumps, intestinal obstruction postoperatively, malnutrition, and infection were factors found to be of etiological importance in the development of pancreatitis. An analysis of factors affecting mortality indicates that hepatic and renal dysfunction augur a fatal prognosis.

Courtesy of References and Reviews
Journal of the American Medical Association

Frey, C., and Redo, S.: Pediatrics 32:93, 1963.

Superfluity of lecturing causes ischial bursitis. — Osler



Book Reviews

Books are those faithful mirrors that reflect to our mind the minds of sages and heroes. — Gibbon

RYPINS' MEDICAL LICENSURE EXAMINATIONS — **Arthur W. Wright, M.D., 10th Edition. J. B. Lippincott Company, Philadelphia, 10th Edition, Copyright 1965, 817 pages.**

This book was originally published in 1933, has been periodically revised and brought up-to-date, and is now in its 10th edition. Its primary purpose is to present a review of the major fields in basic science and clinical fields for the use of the candidate taking state license medical examinations. The text is divided into two parts, Part One, Basic Sciences, including sections on Anatomy, Physiology, Biochemistry, General Microbiology, Pathology and Pharmacology; Part Two, Clinical Sciences, including Surgery, Internal Medicine, Obstetrics and Gynecology, Preventive Medicine and Public Health, and Psychiatry. Each section consists of short, concise discussions of factual material in the particular field, followed at the end of each section by a series of questions designed to test the knowledge of the reader based on the text material presented. Theoretical and practical material are both presented. The clinical sections contain clinical findings, diagnosis, and treatment; and where applicable, basic pathophysiology is also included. A separate section is presented describing and outlining the types of examinations held by the national boards and various state boards, and also some discussion in regard to the preparation and policy relating to the examinations.

In general the book is extremely comprehensive, presenting a wide scope of material, yet eliminating all but the most essential information likely to be asked for in examinations. The text is clearly written by experts in the field. It not only concentrates on important material but also serves as an easily usable broad reference text. A separate section on Pediatrics is not included, although Pediatric Surgery is covered in the Surgery section and much of Pediatric Medicine can be found in the section on Internal Medicine. Tables and charts are used where they help clarify the text; no photographic or illustrative material is otherwise included.

The material is clearly and well presented and in my opinion is an excellent general preparation for the taking of not only state board examinations but any other examination covering wide areas of medicine and basic science. The book is also an excellent reference source with quickly and readily accessible information. Certainly anybody planning to take basic science or state board examinations would be well advised to read this book.

Alvin L. Schultz, M.D.
Minneapolis, Minnesota

VITREORETINAL PATHOLOGY AND SURGERY IN RETINAL DETACHMENT — **Paul A. Cibis, M.D., St. Louis. C. V. Mosby Co. 1965. Illustrated, 293 pages, index, references, Price $20.00.**

The author, now deceased, has presented his experiences in the fast developing field of modern surgery of retinal detachment. The volume is divided into sections dealing with anatomy and physiology, including experimental observations; the various disease states and syndromes; and finally surgical techniques. The author pioneered in a number of newer techniques including vitreous surgery using the silicone liquids. It is indeed fortunate for students of this subject that Dr. Cibis was able to record so lucidly his experiences in the field before his untimely death.

William S. McClanahan, M.D.
Minneapolis, Minnesota

CURRENT MEDICAL TERMINOLOGY — **Third Edition. Edited by Burgess L. Gordon. Published by American Medical Association. Chicago, 1966. 969 pp. Price $4.00.**

Current Medical Terminology is advertised as a reference system for the selection of preferred medical terms and synonyms . . . convenient, current, and timely. It is obviously timely and current, but to describe it as convenient abuses the word. The book is written in computer language: All caps; # is a colon; a small square, a semicolon. This is a step in the direction of computer medicine. A key word, a symptom, a sign, a laboratory reaction will set the wheels (or rather the magnetic tape) in motion and the diagnostic possibilities will appear. Thus in the key word section under "Jaundice" there are 100 entries followed by 100 numbers. One needs only to refer to another section, look up the numbers and find 100 diagnostic possibilities. With a computer available, obviously the whole process would be complete in a few milliseconds. Lacking that gadget, working from section to section, the patient would die before the task was completed. The reaction of this reviewer # THIS MARRIAGE OF MEDICINE TO THE COMPUTER HAS SPAWNED # A BASTARD.

Reuben Berman, M.D.
Minneapolis, Minnesota

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Special Article

The Positive Pap Smear*

MALCOLM B. DOCKERTY, M.D.**
DAVID C. DAHLIN, M.D.**
Rochester, Minnesota
K. A. PREM, M.D.†
G. J. D'ANGIO, M.D.‡
Minneapolis, Minnesota

LONG BEFORE Broders defined, described, and illustrated the microscopic picture of carcinoma in situ in 1932, gynecologists and pathologists occasionally had observed worrisome lesions of this type in the uterine cervix. The lesions were not termed "cancer" because they lacked the invasive qualities which, at that time, were considered necessary before a diagnosis of malignancy could be justified.

Cancers of the cervix were supposed to be at least visible, if not palpable. Accordingly, in the period 1932 through 1946 Broders and his associates made biopsies of every type of uterine cervical abnormality that they could see, and they discovered 32 examples of in-situ carcinoma of the cervix among the thousands of lesions sampled. For every in-situ cancer found, they saw and treated perhaps more than a hundred clinical cancers of the uterine cervix. If any relationship existed between in-situ and overt carcinomas, it was not apparent on the basis of their methods of study.

About that time, the late Dr. George Papanicolaou, while employing a special stain for studying exfoliated cells in vaginal secretions from patients with infertility problems, began to find dark-staining elements which he could not name. His careful observation and follow-up studies led him to the discovery that these abnormal cells had their sources in the lesions which Broders had described. The selfsame elements appeared also to be cast off from clinical cancers of the cervix. Evidence suggested that in-situ lesions were, in fact, early cancers.

A stampede followed. Every conceivable body orifice was scrubbed, scraped, washed, brushed, siphoned, and massaged for its maximal yield of cells, some of which might be malignant. Studies were conducted in which the efficiency of the smear technique was compared with that of biopsy. The problems of "false positive" smears were cussed and discussed. Theoretic and actual relationships between in-situ cancers and clinical cancers were expressed—statistically and otherwise. Terms like "precancer" were resurrected to explain the occurrence of suspicious smears of dubious cellular parentage. From a welter of reports on these and allied aspects of the problems posed by smears, two practical observations emerged: (1) smears are extremely valuable in detecting pulmonary and uterine cancer, and (2) smears can be successfully employed in the discovery of nearly 100% of cervical cancer in the in-situ stage. In our own experience, the yield when the smear is used is perhaps 50 times that obtained by using the method of selective biopsy.

Continued

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*Presented at the 112th Annual Meeting of the Minnesota State Medical Association, May 17, 1965, Minneapolis, Minnesota.

**Mayo Clinic and Mayo Foundation.

†Department of Obstetrics and Gynecology, University of Minnesota Medical School.

‡Division of Radiation Therapy, University of Minnesota Medical School.

How To Make a Smear

In gynecology, *exfoliative cytology* has its greatest usefulness in the detection of preclinical, asymptomatic carcinomas of the uterine cervix. These invisible lesions nearly always begin in the squamous epithelium at its junction with the glandular epithelium of the endocervix. This zone, usually in the region of the cervical external os, can be visualized, and scrapings can be taken directly. The Ayre wooden spatula has two prongs, shaped so that one prong can be inserted into the os while the other scrapes cellular material from the entire circumference of the adjacent exocervix. Perhaps less efficient is an ordinary tongue blade, because of its shape, or a cotton applicator stick, because it absorbs some of the cell-containing secretions.

A combination of endocervical aspiration material and cervical scrapings can be placed on one slide. Although some physicians prepare smears from one patient on several slides, one well-prepared smear is probably adequate. To facilitate examination, the material must be smeared evenly on the slide in one or two strokes. Excessive smearing of the material distorts cells and allows drying of cells before fixation. Immediate immersion in fixative is mandatory, since drying destroys cytologic details. Ethanol (95%) or several other solutions of alcohol or alcohol and ether produce satisfactory fixation.

Procedure when Smear is Positive

Most pathologists report the diagnosis of a smear in categories: classes 1 through 5 which indicate normal, slightly suspicious, suspicious, very suspicious, or malignant cells present, respectively. When there is no clinical evidence of cancer, a class 3 smear report from our laboratory indicates a 50% chance of cancer actually being present, and a class 5 report indicates a nearly 100% chance. Almost all of these preclinical cancers are in-situ lesions of the cervix.

Tissue must be procured from the entire circumference of the junctional zone. Instrumentation, including even the taking of office biopsies, may destroy the histologic evidence of early lesions which often involve only a fraction of the circumference. Accordingly, endocervical and endometrial scrapings should be procured only after the cone is taken. Good rapid-frozen technique allows immediate analysis of these specimens so that any indicated definitive therapy can be accomplished promptly.

The Gynecologist Looks at the Pap Smear

The value of the vaginal (Papanicolaou) smear as an aid in the detection of cancer of the female reproductive tract in general and the uterine cervix in particular has been proved beyond doubt. In the clinician's office, it is most efficiently used for three purposes.

As a Screening Tool

The practicing physician uses the smear most frequently as a general evaluation procedure in the asymptomatic gynecologic patient to complement the routine pelvic examination. This is done to detect exfoliated malignant cells of early nonvisible and nonsymptomatic cancer of the uterus. When an abnormal smear is reported under these circumstances, certain well-defined steps must be taken by the clinician. If the smear is suspicious, a repeat smear is always indicated with or without multiple cervical biopsies; if the smear is positive, multiple biopsies are mandatory. These biopsies can and should be taken in the office with punch-biopsy forceps; hospitalization is unnecessary. Bleeding is controlled if necessary by a vaginal pack or pressure on the bleeding point. If a diagnosis on which treatment can be based cannot be made from the tissue removed at biopsy, a cervical conization and curettage in the hospital, with the patient under anesthesia, is necessary before treatment is prescribed. The need for these surgical procedures emphasizes that *the smear is not a diagnosis* and identifies neither the origin nor the extent of the cancer.

As a Complement to Biopsy

When pelvic findings suggest the possibility of cervical malignancy, both a biopsy and a smear should be taken. The accuracy of the two techniques combined is greater in the detection of cervical malignancy than is either alone. If intrauterine malignant disease is suspected, a smear should also be taken and curettage performed. Conization is indicated if biopsies are inconclusive of the presence or absence of malignancy in the cervix.

As a Follow-up for Treated Carcinoma

A vaginal smear is essential as a routine in the evaluation at each follow-up examination of women treated surgically or radiologically for cervical cancer. A smear will detect abnormal cells prior to gross tissue change visible to the naked eye. These smears detect only local recurrence and not metastases elsewhere in the body. Benign cells on the smear from an irradiated patient may show bizarre changes secondary to irradiation, years after completion of therapy. Under no circumstances should the patient be subjected to further treatment on the basis of an abnormal smear unless there is tissue evidence of recurrent cancer.

Before a smear is regarded as a false-positive one, all procedures available for the detection of the occult cancer must be exhausted. Carcinoma of the fallopian tube and the ovary must be seriously considered as a possibility if the abnormal smear persists and there is no other explanation. Infections may be responsible for the false-suspicious or false-positive smears; in these cases, the smears revert to negative after the infection subsides.

False-negative smears have been reported in up to 10% of cervical cancers. For this reason, a single negative smear should not be accepted by the physician or patient as necessarily indicative of the absence of malignant disease if a suspicious lesion or symptoms are present.

Radiotherapy in Patient with Positive Pap Smear

In the young patient with a positive smear and carcinoma *in situ,* total hysterectomy and intracavitary radium therapy are both acceptable forms of treatment. Both can be expected to give equally good results. If the patient is in the child-bearing age and still wishes to have children, therapy can be deferred as long as continual careful observation is provided. There is an alternative to such a policy: the cervix can be treated, with an intravaginal cone, with kilovoltage techniques, coupled with surgical replacement of the ovaries laterally to ensure minimal radiation to these organs. Delivery of 6,000 rads in five to six weeks to the cervix alone with this technique permits high-dose radiotherapy to the involved area while minimizing the dose to all other pelvic organs and structures.

The patient with a positive smear who, on biopsy, is proved to have invasive carcinoma of the cervix requires treatment appropriate for the lesion as staged according to the League of Nations classification. With few exceptions, radiotherapy is the method of choice.

Consensus of Discussion

In the question-and-answer period which ensued, certain points of agreement and disagreement were presented.

It was the consensus of the essayists that, when unchecked, in-situ carcinoma of the cervix progressed to the clinical phase of the disease. Several agreed with the concept of Stewart that clinical cervical carcinoma could arise in no other way. The calculated average duration of the in-situ phase was perhaps in excess of 10 or 15 years. In certain regions with stable populations, screening programs with the smear technique have resulted in the discovery of many in-situ carcinomas of the cervix. In these same regions the incidence of invasive cervical carcinoma has recently shown a sharp decrease.

It was unanimously agreed that changes in the cervix due to pregnancy never imitate those due to carcinoma in situ and that a positive smear in a pregnant woman is of great significance. Opinions differed as to how one should proceed in establishing the tissue diagnosis in these cases, with some insisting on conization and others, on four-quadrant biopsies. With the diagnosis of infiltrating carcinoma for practical purposes excluded by biopsy, the urgency for conization was argued against the policy of watching the patient until after delivery. It was pointed out that the trauma of vaginal delivery may sometimes destroy a small focus of in-situ carcinoma of the cervix.

The young woman with one of these "in-

Continued

visible" cancers of the cervix can often be treated by simple conization. There is some morbidity associated with the operation and the patient must return periodically for further smear studies. However, approximately 50% of in-situ squamous cell carcinomas extend for variable distances into the endocervix. In these instances, residual carcinoma may remain following anything but a deep conization. Postoperative smears, fortunately, lead to discovery of these residua, and additional, more radical treatment will still effect a cure.

Finally, it was again pointed out that a screening program for the detection of early and curable cancer of the cervix by the smear technique is a team project. Reading the smears is a time-consuming job which requires very special training. Improperly made smears should be reported as unsatisfactory with a "repeat" requested. The reports should be "negative," "suspicious," or "positive." The pathologist should establish his criteria so that the first and last categories are truly meaningful; the middle category should be kept to a reasonable minimum. Should a large proportion (more than 70%) of patients in the "suspicious" category prove not to have carcinoma, the pathologist is causing the patient and the gynecologist undue concern. On the gynecologist's part, it is mandatory that the search for the lesion productive of a positive or suspicious smear be meticulous so that the evidence is not destroyed by the injudicious use of cautery following biopsy. It has been shown that vigorous scrubbing of the cervix preparatory to taking a cone can practically denude the cervix at a site showing in-situ carcinoma.

The Tobacco Tyrant*

Allbut mentions cardiac irregularity and even delirium cordis. Palpitation is common, especially among the young smokers. He says that smoking may cause violent angina which is distinguished from true angina pectoris by "the excessive violence and length of the attacks." He also says that blood pressure rises during smoking and falls below normal after cessation.

Wilson describes two cases of unusually severe anginoid pain which ceased after smoking was discontinued.

Kulbs describes arrhythmia, extrasystoles, and tachycardias, especially in the young. After the age of 50 there may arise symptoms of angina and aortalgia. In the interval between the attacks, bradycardia is more common than tachycardia.

John found an increase in both systolic and diastolic pressures during smoking, which was followed by a fall, lasting two hours, on cessation.

Pozzi & Clerc studied the effects of nicotin on cardiac rhythm in animals. They divided these into an initial bradycardia and a later tachycardia phase. In the former, they occasionally noted auricular arrest with ventricular arrhythmia, and less frequently auricular fibrillation. With tachycardia they observed lessened auriculo-ventricular dissociation.

To be continued next issue.

E. O. Giere, M.D.**
Minneapolis, Minnesota

Editor's Note: In 1928 Dr. E. O. Giere prepared and presented a manuscript at one of the Twin City hospitals on the evil effects of tobacco.

***Through the courtesy of his sons, Doctors Richard and Joe Giere, the timeworn and faded manuscript was made available to the editor. Excerpts will be printed serially.*

See Minnesota Med 48:1687, 1965 and 49:969, 1966.

Maybe everybody should swap problems. The other fellow's are always easier to solve. — Changing Times

History of Medicine

George Washington: His Death and His Doctors

> *"The comparison of what we can do with what we are expected to do is often mortifying enough. But it cannot be helped. People are free to expect what they like; while we cannot do more than can be done."*
>
> *Peter Latham, M.D.*
> *Lectures in Clinical Medicine, 1836*

ON THE EVENING of December 12, 1799, George Washington complained of a cold. Two days later he was dead. The American public, accustomed to the image of Washington as a man of health and vigor, received the news with stunned disbelief. This emotion soon turned to angry questioning of the treatment given by his three physicians. The public's attitude is reflected in a historian's statement: "There can scarcely be a doubt that the treatment of his last illness by his doctors was a little less than murder."[1]

This paper defends Washington's doctors and sets forth the argument that their actions were in keeping with the best medical practice of the times.

Sources

Two eyewitness reports of Washington's death exist. One was recorded in a personal diary by his secretary, Colonel Tobias Lear; the other was a newspaper account in the *Alexandria Times* and was written by two of his three physicians. Both were set down within five days of his death, and they differ little in detail. The state of Washington's health before his fatal illness has been gathered from his diaries and from his biographers. My information about medicine in the 18th century has been collected from dark corners which will be cited in the text. Lastly, I have been aided in interpretation of the events of Washington's final illness by two accounts of the subject.[2,3]

Washington's Health Before His Final Illness

George Washington was no stranger to disease or doctors. He was plagued by a series of illnesses, which started at the age of 16, when he had a bout of "ague* and fever, which I have had to extremity."[4] Three years later, while accompanying his consumptive brother, Lawrence, on a trip to Barbados, he was "strongly attacked with the smallpox."[5] He was nursed back to health, and contrary to popular belief, the disease left only a few insignificant scars on his nose — not a pockmarked face.[6]

After Washington's return to Virginia, he suffered a "violent attack of pleurisy which reduced me very low."[7] He feared that he had contracted his brother's tuberculosis, but his worry proved groundless. In 1755, he joined General Braddock of the British Army for a wilderness campaign against the French and Indians, but he was unable to march because of a four-day illness punctuated by waves of fever. His disease, he tells us, "was relieved by the General's ordering a physician to give me Dr. James powder** one of the most excellent medicines in the world."[7]

The fever returned in 1757 and was complicated by "bloody flux"-dysentery.[8] His physician, Dr. James Craik, an Edinburgh graduate who was to attend him in his fatal illness, advised him to retire from the army. He returned to Mount Vernon, but his symptoms persisted, and he wrote: "At certain periods, I have been reduced to great extremity and have much reason to apprehend an approaching decay. . . ."[7] Washington was morbidly pessimistic about all his

Continued

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*Ague, according to the *Oxford Universal Dictionary*, is a word which originally denoted an acute fever, but subsequently came to mean the paroxysmal fevers of malaria.

**James powder was a mixture of antimonious oxide and calcium phosphate which induced sweating.

illnesses — not an unrealistic attitude in an age in which the life expectancy was less than 40.

A febrile illness in 1761 started with a "violent cold" and lasted for seven to eight months. After he recovered he ventured the dark opinion: "I was very near my last gasp . . . I once thought the grim King would overcome my best efforts and that I must sink in spite of a noble strength."[7] In 1768 he experienced another bout of dysentery, and a Dr. Rummey stayed with him for two evenings. He seems to have rallied nicely, for in a diary entry entitled "Where and How My Time was Spent," written shortly after his illness, he says that he had hunted foxes for 49 days, went to church for 15 days, paid many visits, attended two balls, three plays, one horse race; hunted ducks and played a quantity of cards.[5]

Washington had no serious illnesses during the nine years of the Revolutionary War. After the war in 1786, he had another attack of ague and fever which was relieved by Cinchona bark* prescribed by Dr. Craik.[2] During his presidency, which lasted from 1788 to 1796, Washington had three illnesses. The first occurred shortly after he assumed office and was a carbuncle on his left hip which incapacitated him for six weeks. He was treated by Samuel Bard, a well-known New York practitioner, who in 1771 had written a classical paper on "Angina Suffocativa."[9] In 1790, Washington had a "violent affection of the lungs, the cough, the pain in my breast, shortness of breath."[5] The last illness of his presidency occurred in 1793. Thomas Jefferson wrote to James Madison: "The president is not well; little lingering fevers have been hanging about him for a week or ten days and affecting his looks most remarkably." But Washington regained his strength, and his fever disappeared after a vacation at Newport, Rhode Island.

Washington's Last Years

Washington retired to Mount Vernon in March of 1797. His estates had been neglected during his eight years as president, and he was anxious to resume the duties of a gentleman farmer. He was 65 years old and was still a tall and sturdy figure who daily rode 15 miles around his estates. He weighed over 200 pounds and stood six foot three inches. When he was not supervising his estates, Washington enjoyed convivial gatherings over well-filled glasses of Madeira or hunting for canvasback ducks and foxes.

Washington's decision not to run for a third term was partially dictated by the infirmities of age. His hearing had become increasingly bad — possibly because of his previous treatment with Cinchona bark. He had worn glasses since 1780, and his ill fitting primitive dentures caused him torment and gave him the snaffle-mouth look which Gilbert Stuart had captured in his 1796 portrait of Washington — a picture immortalized on the dollar bill.

Washington's health was good during his retirement except for two febrile illnesses. In August of 1798, he wrote of a sickness which ". . . commenced with a fever on the 19th and lasted until the 24th which left me debilitated."[7] Later that year, he commented on "debilitated health occasioned by a fever which deprived me of 20 pounds of weight."[7] His diary for the remainder of 1798 and for 1799 indicated a restoration of health.

Last Illness

On Thursday, December 12, Washington spent several hours on horseback, riding about and giving directions to his overseers. The weather was bad. Snow, mixed with rain and sleet, drenched Washington. When he returned home, Tobias Lear observed that his neck was wet and that snow was lodged in his hair. On Friday, Washington did not venture out in the morning because of a cold and severe sore throat, but he stepped out onto his front lawn in the afternoon to mark trees to be cut. He spent the evening reading and talking with his family. Because of his increasing hoarseness, Lear suggested he take something for his cold. His reply was "No, you know I never take anything for a cold. Let it go as it came."[2]

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*Cinchona bark was named by Linnaeus in 1742 after the Countess of Chincon, who, when vice-queen of Peru, was cured of fever by Peruvian bark, and afterwards brought a supply of it into Spain. In 1800, quinine was prepared from Cinchona bark.

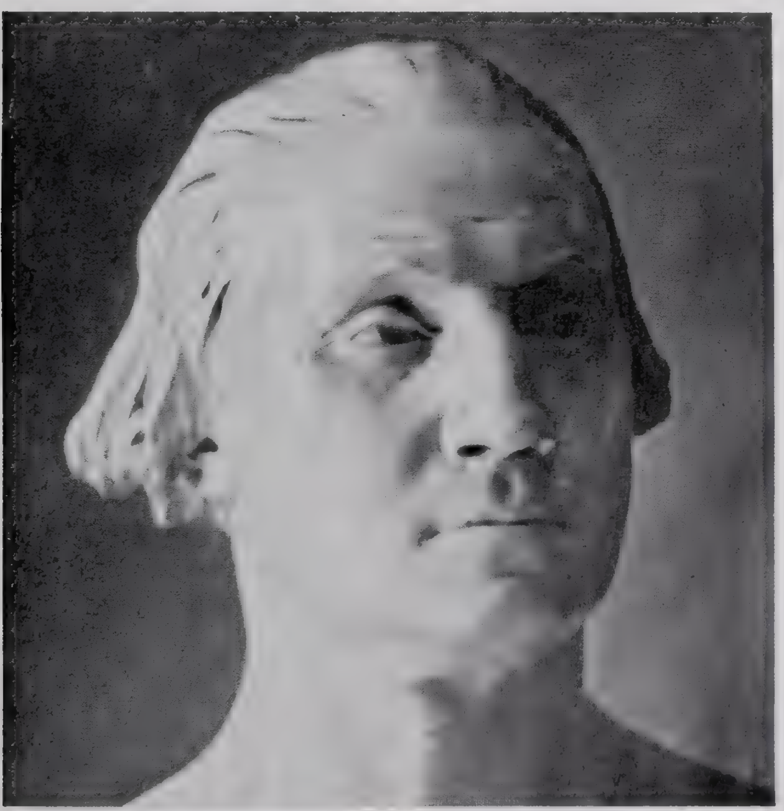
During the night he became rapidly worse with a high fever and pain in the throat. He developed difficulty swallowing with rapid respirations, and he was barely able to speak. At seven in the morning, Mrs. Washington called for Tobias Lear. He was shocked by Washington's appearance. According to Lear's diary: "A mixture of molasses, vinegar and butter was given, but he could not swallow a drop, and when he attempted, he appeared to be distressed, convulsive and almost suffocated."[2]

At Washington's request, Rawlins, an overseer, was sent for, and a pint of blood was taken without relief. Lear then applied sol volatile to his neck, and the patient complained of a tender neck. Because of his worsening condition, Lear dispatched his own servant for Washington's old friend, Dr. Craik who lived nine miles away in Alexandria. Shortly thereafter messengers were sent to summon Doctors Gustavus Brown and Doctor Elisha Dick.

The Doctors

Dr. James Craik arrived at Mount Vernon at about eleven o'clock in the morning. He was two to three years Washington's elder and had been his physician and social companion for at least 35 years. Dr. Craik was a Scotsman and a graduate of Edinburgh — a school which supplied America with 117 M.D.s before 1800.[3] He made a diagnosis of "inflammatory quinsy" and applied a blister of canthrarides to the throat, and did a second bleeding. Understandably, he was anxious for consultation, and he awaited the arrival of the other physicians. At 3 o'clock, Doctor Dick came, and Doctor Brown soon after.

Dr. Dick was 37 years old and a graduate of the University of Pennsylvania —



GEORGE WASHINGTON BY JEAN ANTIONE HOUDON (detail). This version of Houdon's 1784 bust belonged to Thomas Jefferson. It presents the hero vividly as a virile athletic man. Courtesy of the Boston Athenaeum. Photograph by H. H. Arnason.

Continued

founded in 1765. He had served his apprenticeship under Dr. Benjamin Rush and Dr. William Shippen — probably the two most famous physicians of America. He suggested a tracheostomy and cessation of further bleeding. Tracheostomy had not yet been performed in the colonies, and they elected not to undertake the operation on their illustrious patient. By the time Dr. Brown, another Edinburgh graduate, arrived, Washington could swallow, and the three physicians decided on symptomatic treatment. They administered a dose of calomel and tartar emetic.

Washington, sensing the end was near, asked his wife to bring him his wills. At 5 o'clock p.m. he sat up in a chair for one-half hour. He was obviously in great pain and had difficulty breathing. He never lapsed in an unconsciousness, but his breathing grew "imperfect." He expired between 10 and 11 p.m. on December 14 — 17 days before the dawn of the 19th century.

Statement to the Press

Doctors Craik and Dick submitted this statement to the *Alexandria Times* where it was published on December 19, 1977. It was subsequently reprinted in the *Medical Reposition,* founded in 1797, and the first medical journal of the colonies.

> "Presuming that some account of the late illness and death of General Washington will be generally interesting, and particularly so to the professors and practitioners of medicine throughout America, we request you to publish the following statement.
>
> Some time in the night of Friday, the 13th inst., having been exposed to rain on the preceding day, General Washington was attacked with an inflammatory affection of the upper part of the windpipe, called in technical language, cynanche trachealis. The disease commenced with a violent ague, accompanied with some pain in the upper and fore part of the throat, a sense of stricture in the same part, a cough, and a difficulty rather than painful deglutition, which were soon succeeded by fever and a quick and laborious respiration. The necessity of bloodletting suggesting itself to the General, he procured a bleeder in the neighborhood who took from the arm in the night, twelve or fourteen ounces of blood; he would not by any means be prevailed upon by the family to send for the attending physician till the following morning, who arrived at Mount Vernon at eleven o'clock on Saturday morning. Discovering the case to be highly alarming, and foreseeing the fatal tendency of the disease, two consulting physicians were immediately sent for, who arrived one at half past three and the other at four in the afternoon. In the interim were employed two copious bleedings; a blister was applied to the part affected, two moderate doses of calomel were given, an injection was administered which operated on the lower intestines, but all without any perceptible advantage, the respirations becoming still more difficult and distressing. Upon the arrival of the first of the consulting physicians, it was agreed as there were yet no signs of accumulation in the bronchial vessels of the lungs, to try the result of another bleeding, when about thirty two ounces were drawn, without the smallest apparent alleviation of the disease. Vapours of vinegar and water were frequently inhaled, ten grains of calomel were given succeeded by repeated doses of emetic tartar amounting in all to five or six grains, with no other effect than a copious discharge from the bowels. The powers of life seemed now manifestly yielding to the force of the disorder. Blisters were applied to the extremities, together with a cataplasm of bran and vinegar to the throat. Speaking, which was painful from the beginning, now became almost impracticable, respirations grew more and more contracted and imperfect, till half after eleven o'clock on Saturday night, when, retaining the full possession of his intellect, he expired without a struggle.
>
> He was fully impressed at the beginning of his complaint as well as through every succeeding stage of it, that its conclusion would be fatal, submitting to the several exertions made for his recovery, rather as a duty than from an expectation of their efficacy. He considered the operation of death upon his system as a coeval with the disease and several hours before his decease, after repeated efforts to be understood, succeeded in expressing a desire that he might be permitted to die without interruption.
>
> During the short period of his illness he economized his time in the arrangement of such few concerns as required his attention with the utmost serenity, and anticipated his approaching dissolution with every demonstration of that equanimity for which his whole life had been so uniformly and singularly conspicuous."
>
> James Craik
> Attending Physician
>
> Elisha C. Dick
> Consulting Physician
>
> The signature of Doctor Gustavus Brown, of Port Tobacco, who attended as consulting physician, on account of the remoteness of his residence from the place, has not been procured to the foregoing."

Treatment

Before any judgement can be made concerning Washington's treatment, the practice of medicine of the period must be understood. The Art outstripped the Science, and the classification of disease was a welter of conflicting systems. At one pole was William Cullen's doctrine of all diseases as nervous disorders and at the other was the dogma of John Brown, (1735-1788), who claimed that all diseases were due to an imbalance of stimuli. Brown, a coarse, disreputable man, classified all diseases as "sthenic" or "asthenic" and his treatment consisted of opium or alcohol — depending on the diagnosis. Morgagni's monumental treatise, *De Sedibus et Causis Morborum,* the bedrock of Pathological Anatomy, appeared in 1761; but it was in Latin and was probably unread by most American doctors.

At the time of Washington's death, auscultation, percussion and palpitation had not been developed and clinical instruments such as thermometers, blood pressure cuffs, stethoscopes, and laryngoscopes did not exist. The practice of clinical medicine rested on the theories of Boorhaave, (1668-1738), Sydenham (1624-89), and Cullen (1712-1790). Cullen was Craik's and Dick's professor at Edinburgh, and it is likely that they were students of his book, *First Lines in the Practice of Physic,* published in 1781.[10]

Cullen's book contained a chapter on Quinsy or Cynanche Trachealis. The following excerpt demonstrates that Washington's physicians followed closely the recommended therapy of Cullen — a recognized authority. Of cynanche treachealis, he writes, "This name has been given to an inflammation of the glottis, larynx or upper part of the trachea, whether it affects a membrane of these parts or a muscle adjoining. It may arise first in these and continue to subsist in them alone, or it may come to affect these parts from the cynanche tonsillaris or maligna spreading into them.

In either case it has been a rare occurrence and a few instances of it have been marked and recorded by physicians. It is to be known by a peculiar croaking sound in the voice, by difficult respirations with a sense of straightening about the larynx, and by an attending pyrexia.

From the nature of these symptoms and from a dissection of the bodies of persons who have died of this disease, there is no doubt of its being of an inflammatory kind. It does not, however, always run a course of inflammation, but frequently produces such as obstruction of a passage of air as suffocates, and thereby proves suddenly fatal.

If we judge rightly of the nature of this disease, it will be obvious that a cure of it requires a most powerful remedy for the inflammation, to be employed upon the first appearance of symptoms. When a suffocation is threatened, whether any remedies can be employed to prevent it, we have not an experiment to determine.

As we suppose the disease to be an inflammatory affection, so we attempt a cure of it by the usual remedies of inflammation, and which for the most part we have found effectual. Bleeding, both topical and general, has often given almost immediate relief, and by bleeding repeatedly has entirely cured the disease. Blistering also near to the part affected, has been found useful. Upon a first attack of the disease vomiting immediately after bleeding seems to be of use, and sometimes removes the disease. In every stage of the disease, an antiphlogistic requirement is necessary, and particularly the frequent use of laxatives. Though we suppose that a spasm of the glottis is often fatal in this disease, we have not found antispasmodic remedies to be of any use."

If Washington's doctors consulted the book of another authority, Thomas Sydenham, they would have found this advice for treating quinsy: "Bleed plentifully in the arm, and let the inflamed parts be besmeared with honey of roses, well acidulated with spirit of vitriol, or spirit of sulphur; and soon after let a gargle be used, not in the common way, but quietly in the mouth till it grows warm, and then spit out. . . Next morning, unless the fever and difficulty be abated, bleeding must be repeated, and purging deferred until the subsequent day, otherwise a gentle purge may be given."[11]

Dr. Elisha Dick's suggestion to perform a tracheostomy was remarkable because, had Brown and Craik complied with his wish, it would have been the first done in America. Among the first to successfully execute the operation was John Andree, a London Surgeon, in 1782, and the account of the subject did not appear until 1812.

In 1833, Trousseau knew of 21 instances of tracheostomy with seven patients saved.[13] Washington's three physicians cannot be blamed for failing to carry through with a tracheostomy. By 1799, there were probably more failures than successes, and they

Continued

would have been condemned had their efforts failed. Tracheostomy was not accepted by the medical profession until Trousseau popularized it in 1833.

Differential Diagnosis

In retrospect, Washington's physician's diagnosis of "cynanche trachealis" appears to be correct. Cynanche was a term applied to all inflammation of the throat and neck. Quinsy, the original diagnosis made by Craik, was also a nonspecific term relating to the throat, and did not, as now, mean peritonsillar abscess.

Doctors of the 18th century had a different view of sore throats than modern physicians. Necrotizing throats were a common fatal complication of scarlet fever, and of such serious illnesses as small pox, typhus, typhoid, and diphtheria. To compound the diagnostic problem, patients were often jammed together in filthy wards, and mixed infections were the rule.

Throat infections occurred mostly in epidemics with a high mortality rate. It appears that Washington's sore throat was not a part of an epidemic. For this reason and because of his age, diphtheria and the scarlet fever localized to the throat probably can be dismissed from the differential — although diphtheria and scarlet fever did occur in adults in that era. W. H. Wells, an otolaryngologist, wrote in 1927 that inflammatory laryngitis, possibly secondary to streptococcal infection, was the most likely diagnosis.[2] R. Scott Stevenson, an English Physician, agrees with the original diagnosis of quinsy.[3] A peritonsillar abscess may well have dissected into soft tissue of the neck, surrounded the larynx, and produced obstruction and death. Whatever the precise diagnosis, Washington's physicians had nothing in their medical bags — except a scalpel — to cure him.

Richard L. Reece, M.D.
St. Barnabas Hospital
Minneapolis, Minnesota

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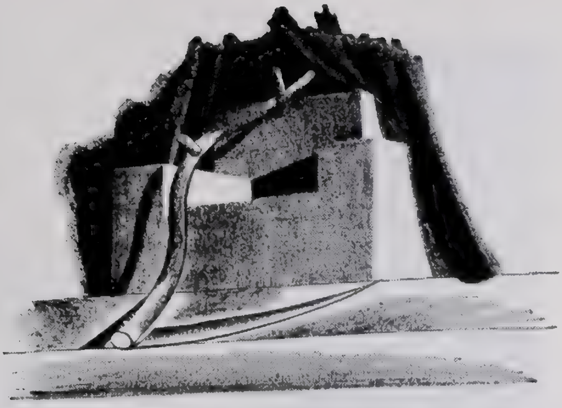
On Being a Patient

You cannot be a perfect doctor, till you have been a patient. You cannot be a perfect surgeon, till you have enjoyed in your own person some surgical experience. Enjoyed, I say, and stick to the word. Count the ways of enjoyment. To be the dear object of so much care and friendship, to be compassed about with hopes and prayers, is there no pleasure in that? To behave nicely, and nothing common do or mean, upon that memorable scene, but lie on the operating-table like Patience on a monument, is there no pleasure in that act of self-control? — Stephen Paget (1855-1926)



In Memoriam

Earth has no sorrow that heaven cannot heal. — Moore

MARSHALL I. HOWARD, M.D.

Dr. Marshall I. Howard, 66, former president of the Mankato Clinic, died March 27. Dr. Howard was born in Iowa, and received his medical degree at the University of Minnesota.

He was a member of the Minnesota Obstetrical and Gynecological Society, Minnesota State Medical Association, and American Medical Association. Dr. Howard was also a past president of the Blue Earth County Medical Society.

He is survived by his wife, a daughter, and a son, Dr. Michael Howard of Chicago.

NELLIE OLEA BARSNESS, M.D.

Dr. Nellie O. Barsness, 92, St. Paul physician and surgeon, died May 12. She was born in Polk County, Minnesota, and had lived in St. Paul sixty years.

Dr. Barsness was a past state health director of the Women's Christian Temperance Union, a member of the Ramsey County Medical Society, American Medical Association and a Life and 50 Club member of the Minnesota State Medical Association. She was also a member of the board of the American Medical Women's Association and the International Medical Women's Association.

She is survived by her son, Dr. Harry Simmonds of St. Paul.

GALEN H. ADKINS, M.D.

Dr. Galen H. Adkins, 57, medical director of the Cambridge State School and Hospital, died April 27, during the night of an apparent heart attack. He had served as superintendent of the Sandstone Institution from 1957 to 1959 after which time he became superintendent at Cambridge. In 1964 he was made medical director of that institution.

Born at Jetmore, Kansas, he received his medical degree at the University of Minnesota Medical School. Dr. Adkins was a member of the East Central Minnesota Medical Society, American Medical Association and the Minnesota State Medical Association.

He is survived by his wife, five daughters and a son.

CARL R. BUTTURFF, M.D.

Dr. Carl R. Butturff, 82, physician at Freeborn since 1906, died April 1, after a long illness. A native of Marshall, he received his doctor of medicine at the University of Minnesota Medical School. Dr. Butturff practiced thirty-seven years in Freeborn before his retirement in 1949.

He was a member of the Freeborn County Medical Society, American Medical Association and a 50 Club and Life member of the Minnesota State Medical Association.

He is survived by his wife.

MALCOLM ROSSLAND JOHNSON, M.D.

Dr. Malcolm Johnson, 54, Minneapolis ophthalmologist, died May 21. Born in Willmar, Minnesota, he graduated from the University of Minnesota Medical School in 1935.

Dr. Johnson was a member of the American College of Surgeons, the American Academy of Ophthalmology and Otolaryngology, Hennepin County Medical Society, Minnesota State Medical Association and the American Medical Association. He was on the medical staffs of Swedish, Lutheran Deaconess and Veterans Hospitals.

He is survived by his wife, a son and a daughter.

ROBERT ZEMMERS, M.D.

Dr. Robert Zemmers, 67, Duluth anesthesiologist, died May 14 in a Duluth hospital. Born in Stalbe, Latvia, he came to the United States in 1948. He received his medical education at the University of Latvia Faculty of Medicine and served as a general practitioner in Valmieria, Latvia, becoming chief of the Department of Infectious Diseases at the Valmieria City Hospital before going to the United States.

He was a member of the St. Louis County Medical Society, Minnesota State Medical Association, Minnesota Society of Anesthesiologists, American Society of Anesthesiologists, and the American Medical Association.

He is survived by his wife and a son, Dr. Robert M. Zemmers of Minneapolis.

CHARLES E. MERKERT, M.D.

Dr. Charles E. Merkert, 69, a physician and surgeon in Minneapolis the past forty years, died May 18. Chief of staff of Lutheran Deaconess Hospital, Dr. Merkert was active in several public health associations.

He was a former chairman of the public health committee of the Hennepin County Medical Society, board member of the Minneapolis Surgical Society, member of the American Medical Association and an associate member of the Minnesota State Medical Association.

Born in St. Paul, Dr. Merkert received his medical degree at the University of Minnesota.

He is survived by his wife.

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Meetings and Announcements

The memory is a treasurer to whom we must give funds, if we withdraw the assistance we need. — Rowe

JULY

Rocky Mountain Cancer Conference, July 15-16, at Brown Palace Hotel, Denver, Colorado. Contact: Rocky Mountain Cancer Conference, 1809 East 18th Avenue, Denver, Colorado.

American Veterinary Medical Association, Minneapolis, July 13-18. Exec. Sec.: H. E. Kingman, Jr., DVM, 600 S. Michigan, Chicago.

University of Colorado School of Medicine postgraduate courses: July 11-14, Estes Park on Ophthalmology; July 17-23 for 12th Annual General Practice Review and July 27-29, Aspen on Dermatology. For further information: University of Colorado, 4200 East Ninth Avenue, Denver, Colorado.

Conference on Comparative Aspects of Reproductive Failure, Dartmouth Medical School, Hanover, N. H., July 25-29. Info: Kurt Benirschke, M.D., Dartmouth Medical School, Dept. of Pathology, Hanover, N. H. 03755.

Conference on Medicine and Religion (Presented by University of California Extension), Lake Arrowhead, Calif., July 10-13. Info: Donald Brayton, M.D., 15-39 Rehabilitation Center, West Medical Campus, University of California, Los Angeles 90024.

Idaho State Medical Association, [E], The Lodge, Sun Valley, July 6-9. Exec. Sec.: Armand L. Bird, 360 Sonna Bldg., Boise.

AUGUST

American Academy of Physical Medicine and Rehabilitation, Sheraton Palace Hotel, San Francisco, Aug. 28-Sept. 2. Sec.: Harriet E. Gillette, M.D., Cleveland Clinic, Cleveland.

American Association of Electromyography and Electrodiagnosis, Sheraton Palace Hotel, San Francisco, Aug. 28. Dir.: Max Karl Newman, M.D., 16861 Wyoming Ave., Detroit 48221.

American Congress of Physical Medicine and Rehabilitation, [E, M], Sheraton-Palace Hotel, San Francisco, Aug. 28-Sept. 2. Exec. Dir.: Creston C. Herold, 30 N. Michigan, Suite 922, Chicago 60602.

American Hospital Association, [E], Palmer House, Chicago, Aug. 29-Sept. 1. Exec. Vice Pres.: Edwin L. Crosby, M.D., 840 Lake Shore Dr., Chicago 60611.

Black Hills Fall Seminar, Rapid City, S. Dak., Aug. 5-6. Info: John F. Leeds, M.D., 615 Kansas City St., Rapid City, S. Dak. 57701.

National Medical Association (71st Annual Session), Pick-Congress Hotel, Chicago, Aug. 8-12. Exec. Sec.: John T. Givens, M.D., 2400 Corprew Ave., Norfolk, Va.

Rocky Mountain Radiological Society, Brown Palace Hotel, Denver, Aug. 18-20. Sec.-Treas.: Robert W. Lackey, M.D., 4200 E. Ninth Ave., Denver 80220.

Rehabilitation Nursing Course, August 8 through 26, 1800 Chicago Avenue, Minneapolis. Contact: Jean R. Plass, R.N. at the American Rehabilitation Foundation.

SEPTEMBER

The Annual Fall Meeting of the Northwestern Pediatrics Society will be held on Friday, September 23, at the White Pine Inn, Bayport. Eldon Berglund, M.D. President.

Minnesota Society of X-ray Technologists Annual Meeting, September 30-October 1, Statler Hilton Hotel, St. Paul. Contact: Richard Board, R.T., 416 Marquette Bank Building, Minneapolis.

Second Annual Symposium on Kidney Disease sponsored by the Upper Midwest Chapter of the National Kidney Foundation, St. Paul Hilton Hotel, September 14. Contact: John M. Burns, M.D., 451 North Dunlap, St. Paul.

ANNOUNCEMENTS

Minnesota Surgical Society Annual Essay Prize to be awarded in November, 1966. Prize of $500 will be given for the best paper on a surgical subject submitted by a medical student, intern or resident. Papers directed to surgical research and papers on clinical topics are acceptable. Deadline for submission of manuscripts is August 1, 1966. Send papers to: John F. Perry, Jr., M.D., St. Paul-Ramsey Hospital, 640 Jackson St., St. Paul.

In Appreciation

The Minnesota State Medical Association would like to express its appreciation to the firms listed below. These firms were technical exhibitors during the recent 113th Annual Meeting of your Association. Their participation in our annual meeting contributed much to its success.

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Physician's Diary

The true test of civilization is, not the census, nor the size of cities, nor the crops, but the kind of man that the country turns out. — Emerson

Dr. Gordon Hovde, Chisago City recently was appointed to the Green Acres Nursing Home Board.

* * *

Dr. Oliver H. Beahrs, head of a Mayo Clinic section of surgery, was elected a member of the board of trustees of the Mayo Foundation at its annual meeting.

* * *

Dr. Donald L. Carlson of Moorhead has been elected chief-of-staff at the St. Ansgar Hospital. **Dr. Richard H. Seifert** was elected vice-president, and **Dr. H. G. Rice**, the new secretary-treasurer.

* * *

Dr. Ellis S. Benson, professor of laboratory medicine and biochemistry in the University of Minnesota's College of Medical Sciences, has been named the new head of the laboratory medicine department.

* * *

Dr. Fred A. Lyon of Minneapolis has been installed as a fellow of the American College of Obstetricians and Gynecologists, and **Dr. Paul Hartig** of Minneapolis has been certified as a diplomate of the American Board of Urology.

* * *

Dr. H. E. Michelson of Minneapolis has been elected an honorary member of the Section of Dermatology of the Royal Society of Medicine of London.

* * *

Dr. Arthur M. Olsen of the Mayo Clinic has been reelected president of the Minnesota Tuberculosis and Health Association.

* * *

Dr. A. P. Goblirsch of Sleepy Eye was honored for forty years of service to that community. A plaque honoring him was presented during a dinner held in his honor.

* * *

Dr. Roger I. Lienke of Minneapolis has been elected to a membership in the American Academy of General Practice, and **Dr. Neil D. Nickerson** of Fairmont has been admitted to a full fellowship in the American College of Physicians.

Dr. Richard H. Decker, research associate in the Mayo Clinic section of biochemistry, received a five-year career development award from the National Institutes of Health, and **Dr. Leonard A. Lang**, Minneapolis obstetrician and gynecologist, received an alumni award from the pre-medicine and biological science students at the College of St. Thomas.

* * *

NEW LOCATIONS: **Dr. David S. Berkman**, medical staff physician at the Rochester State hospital, plans to open a private practice of medicine in Emily . . . **Dr. Timothy Nealy** opened a medical practice in Blooming Prairie . . . **Dr. William O. Reid** has joined the Rice Memorial Hospital in Willmar . . . **Dr. Elton Glenn Wing** will join **Dr. E. E. Keithahn** in the practice of medicine in Sleepy Eye . . . **Dr. Elizabeth Rieschl** of Jordon is to be associated with the New Prague Medical Clinic.

* * *

Dr. Robert A. Good, professor of pediatrics and microbiology at the University of Minnesota, received an honorary doctor of medicine degree from the University of Uppsala, Sweden.

* * *

Dr. Richard V. Ebert, professor and head of the department of medicine at the Medical School of the University of Arkansas, will head up the department of medicine in the University of Minnesota's College of Medical Sciences.

* * *

The March issue carried a statement that the Wyeth Pharmaceutical Company had given **Burtrum Schiele, M.D.**, professor in the department of Psychiatry of the University of Minnesota, an unrestricted grant for medical research. Dr. Schiele did receive the check; however, the grant was given jointly to **Dr. Richard Teeter**, Chief of Psychiatry at the St. Paul-Ramsey Hospital, and **Dr. James Janecek**, Chief of the Inpatient Service at the same hospital.

* * *

St. Luke's Hospital in St. Paul celebrated its 111th birthday, May 17. The first building was a small wooden structure near the capitol.

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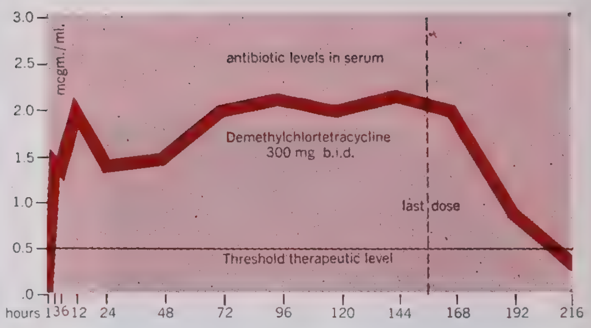

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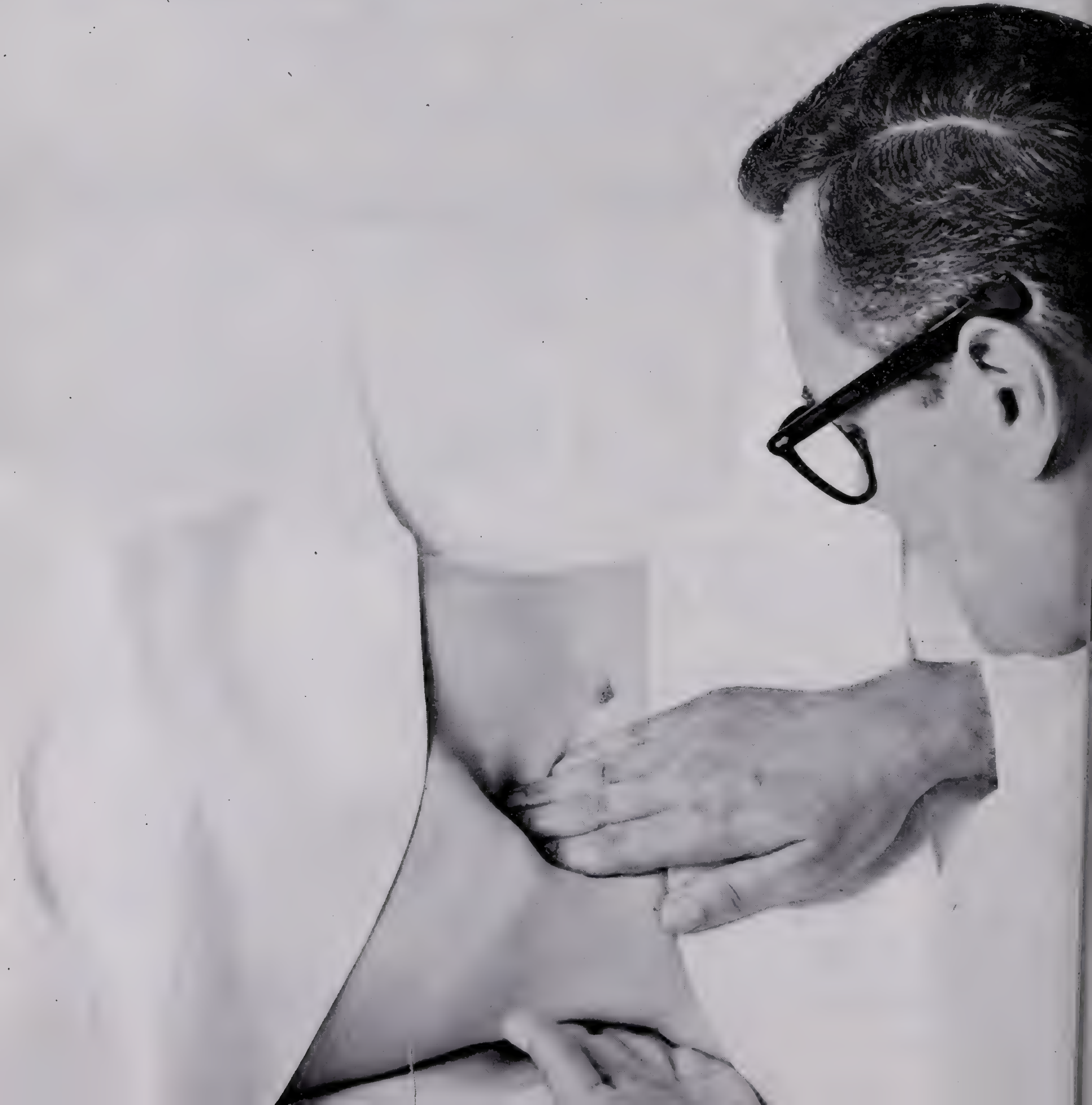

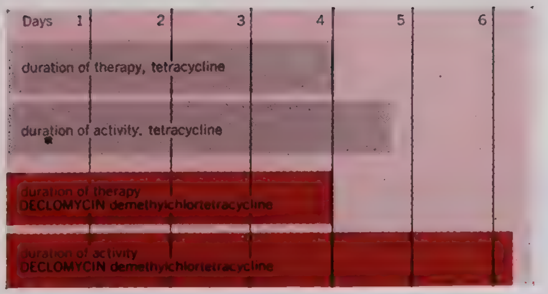

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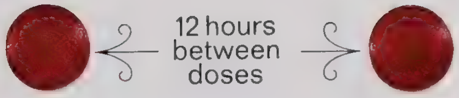

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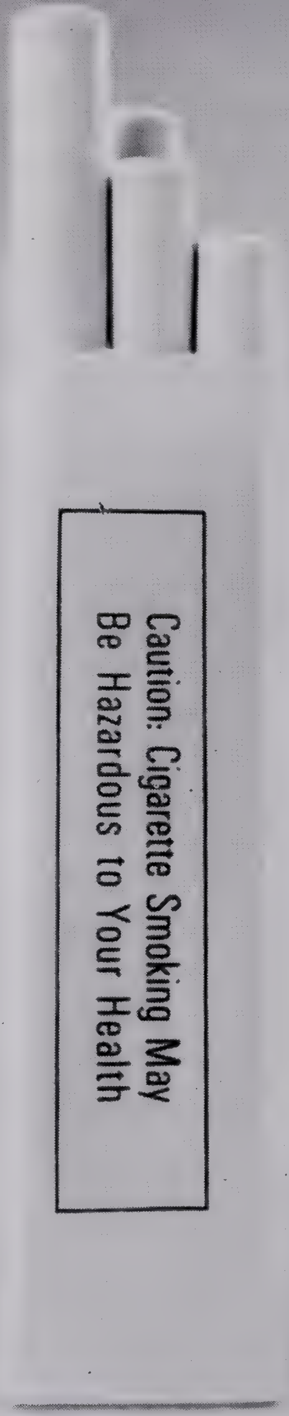

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WANTED: young general practitioner to join six-man group consisting of 4 GPs, a general surgeon, and radiologist. College town of 5,500, 30 miles from Twin Cities. Also need LOCUM TENENS in general practice. Contact: Ed Jenkins, Mgr., River Falls Medical Clinic, River Falls, Wisc. Phone 425-5322.

WANTED: Immediate opening for young GP in an established medical corporation. Three man G.P. group located in rapid-growing North Suburban Metropolitan Area. 15 minutes from loop and large educational center. New clinic. New 150-bed hospital. Salary open, fringe benefits. Fridley Medical Center, P.A., 203 Mississippi Street, Minneapolis, Minnesota 560-2950.

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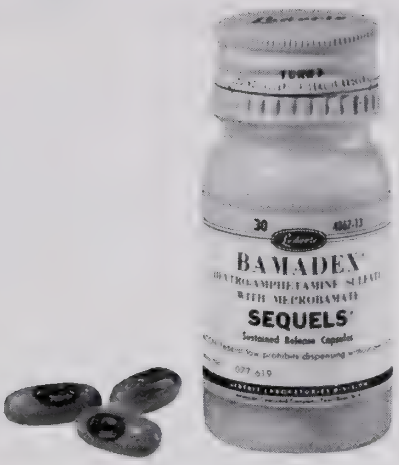

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Minnesota Medicine at a Glance

Exanthem: Echovirus Infection — Wedemeyer et al. Page 1057

In recent years there have been numerous reports of rashes associated with diseases caused by the Echovirus and Coxsackie virus. A case is reported of a one-year-old girl with a febrile illness of three weeks duration, who, with the onset of her illness, developed a fine discrete rash over her face. The rash progressed distally and became a discrete red maculopapular eruption, especially on the distal upper arms and the anterior trunk and legs, and was described as similar in appearance to erythema infectiosum or erythema multiforme. Other findings were: mild generalized lymphadenopathy, anorexia, mild diarrhea, lethargy and mild ataxia. Virological studies demonstrated presence in the stool of Echovirus type 18, and acute and convalescent sera from the patient revealed a fourfold rise in antibody titer to Echovirus type 18.

This is the second case of an exanthematous disease reported in association with Echovirus type 18 infection and indicates the value of virologic study, particularly in atypical exanthematous diseases.

Primary Hyperparathyroidism — Winter et al. Page 1061

Despite a continuing gain in knowledge concerning calcium and phosphorus metabolism, primary hyperparathyroidism persists in presenting some problems in diagnosis. Some of the unusual and occasionally bizarre symptoms of hyperparathyroidism are enumerated in this study of 24 patients. In a case report one patient who apparently had symptoms for a period of 21 years was finally proven to have a chief cell adenoma of the parathyroid. No doubt because of the kidney damage that had been produced over this long period of time, he died from the sequelae of this disease which had not been previously recognized.

Sarcoidosis with Chylothorax — Aberg et al. Page 1065

Sarcoidosis continues to remain ideologically an obscure problem, with an ever increasing variety of clinical manifestations.

The close follow-up of a case reported by Aberg et al. reveals some interesting and unusual findings well worth more extensive scrutiny.

Treatment of Acute Myeloid Leukemia — Kennedy et al. Page 1071

A combined chemotherapeutic regime consisting of 6-mercaptopurine (2.5 mg. per kilo. per day by mouth for five days) and cyclophosphamide (40 mg. per kilo. intravenously in a single dose on the sixth day) was administered to ten patients with leukemia. Two of the patients had had chronic granulocytic leukemia and were in an acute transitional phase. Three patients were classified as having subacute granulocytic leukemia, and four patients, acute granulocytic leukemia. One patient had a myeloproliferative syndrome. An increase in the hemoglobin and platelets was noted in three patients and all had reductions of leukocytes and myeloblasts. Androgens were also used in two of the patients, resulting in an increase of the hemoglobin. Possible metabolic basis for the apparent synergism leaves an interesting thought for further speculation.

Pulmonary Nocardiosis — Yue et al. Page 1077

Nocardiosis is a severe but uncommon fungus disease. Early diagnosis and treatment are necessary for a favorable outcome. Two cases seen at the Glen Lake Sanatorium are presented.

Nocardiosis is most commonly introduced to the body via the respiratory tract. It can proceed in a variety of ways, producing infection, suppuration, and abscess. It frequently resembles very closely a wide variety of other infectious diseases.

Erythroblastosis Fetalis — Adcock Page 1081

The genotype of the father and the obstetrical history, prenatal course and antibody titer levels of the Rh sensitized mother do not provide sufficient information to always determine the severity of erythroblastosis fetalis prior to birth. The study of amniotic fluid bilirubin pigments, however, measures the degree of affectation of the intrauterine fetus and guides its treatment. Intrauterine transfusion may allow maturity of the fetus, and properly timed premature delivery with exchange transfusion can salvage a large proportion of the infants.

Obstructive Airway Disease — Dines Page 1089

A case of emphysema with severe disability and considerable aberration of pulmonary function as determined by a battery of tests was actively treated for one year with high fluid intake, breathing exercises, expectorants, nebulization, bronchodilation, and antibiotics. Significant symptomatic and laboratory improvement occurred.

Agammaglobulinemia — Neuro-Pediatrics Conference Page 1123

Infants suffering from agammaglobulinemia are subject to recurrent bacterial infection caused by primary pyogenic organisms and a variety of other diseases. The definitive diagnosis is dependent upon immunologic tests. There are many other procedures which, if positive, lead to a presumptive diagnosis.

The mental retardation which was observed in this child no doubt resulted from the residue of a meningitis which developed when he was five years old. After this the child made no appreciable advance in mental status, and the problem of further education and a full evaluation of this child's condition is detailed in the Neuro-Pediatrics Conference.

Hypertensive Crisis and Parnate — Crosson Page 1155

Parnate is one of the many monoamine oxidase inhibitors used for the treatment of depression and hypertension, but in prescribing it one must keep in mind the possibility of some side effects in certain individuals who have a metabolism that cannot completely metabolize the tyramine in certain types of cheese.

This is well illustrated in the case report of a woman who was taking tranylcypromine and had for the first time eaten some Cheddar cheese.

There is a Moral Sense and there is an Immoral Sense. History shows us that the Moral Sense enables us to perceive morality and how to avoid it, and that the Immoral Sense enables us to perceive immorality and how to enjoy it. — Mark Twain

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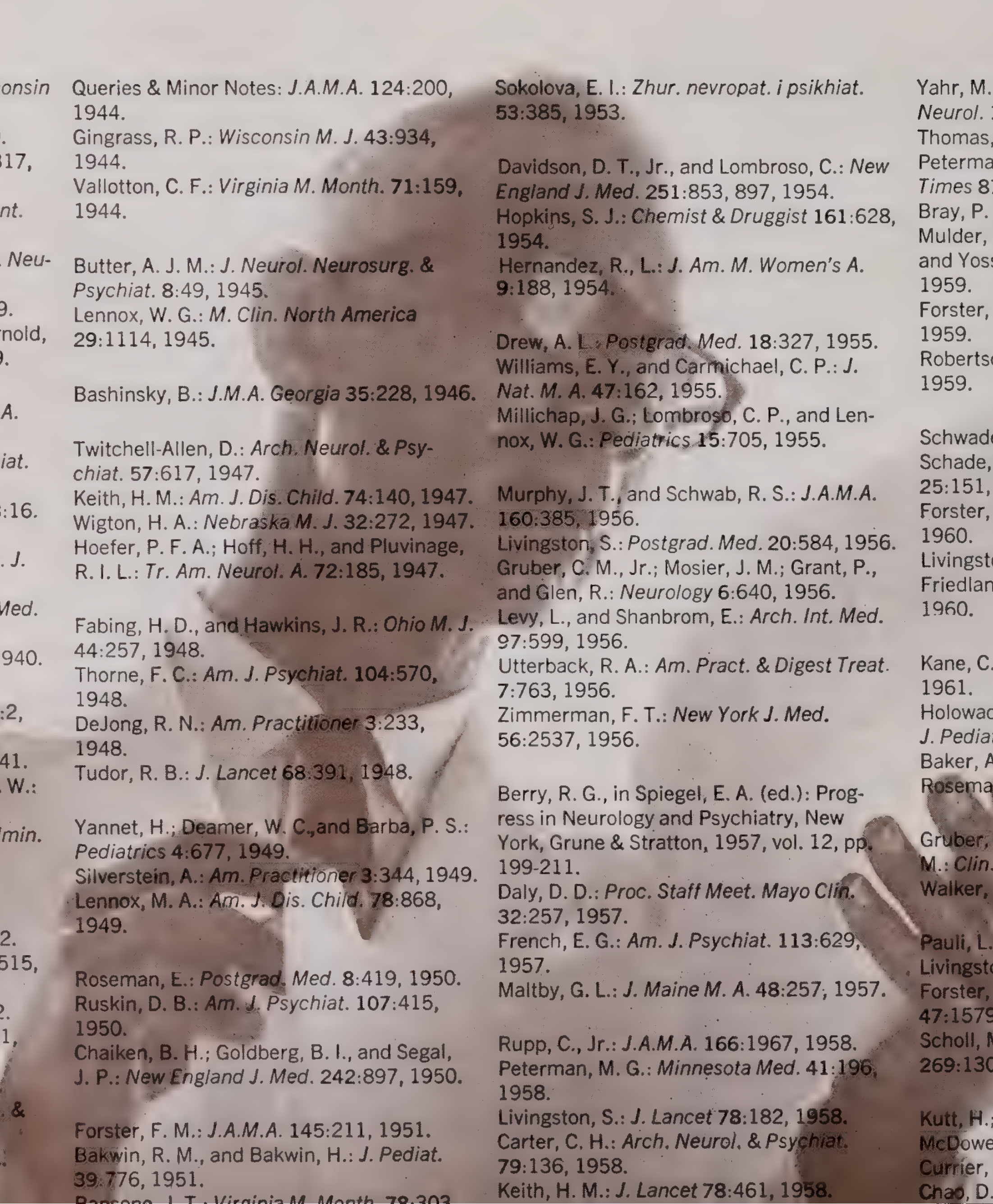

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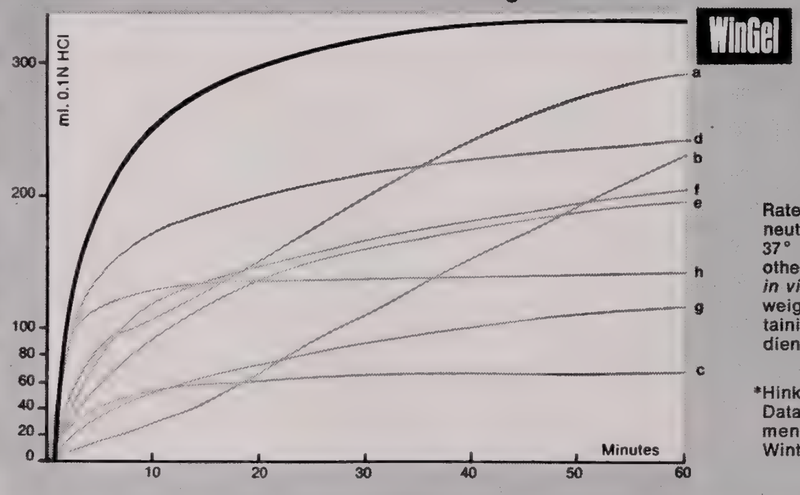

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*Hinkel, E. T., Jr. (New York): Data in the files of the Department of Medical Research, Winthrop Laboratories.

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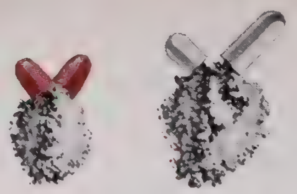
in G.U. infections broad-spectrum performance



greater potency

lower mg intake per day

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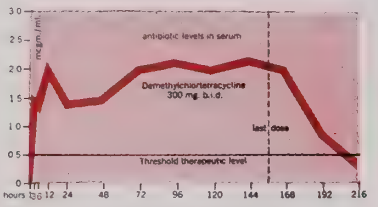

high activity

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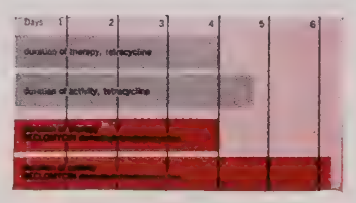
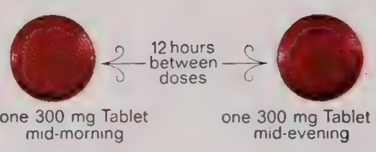


1-2 "extra" days' activity

after the last dose to protect against relapse



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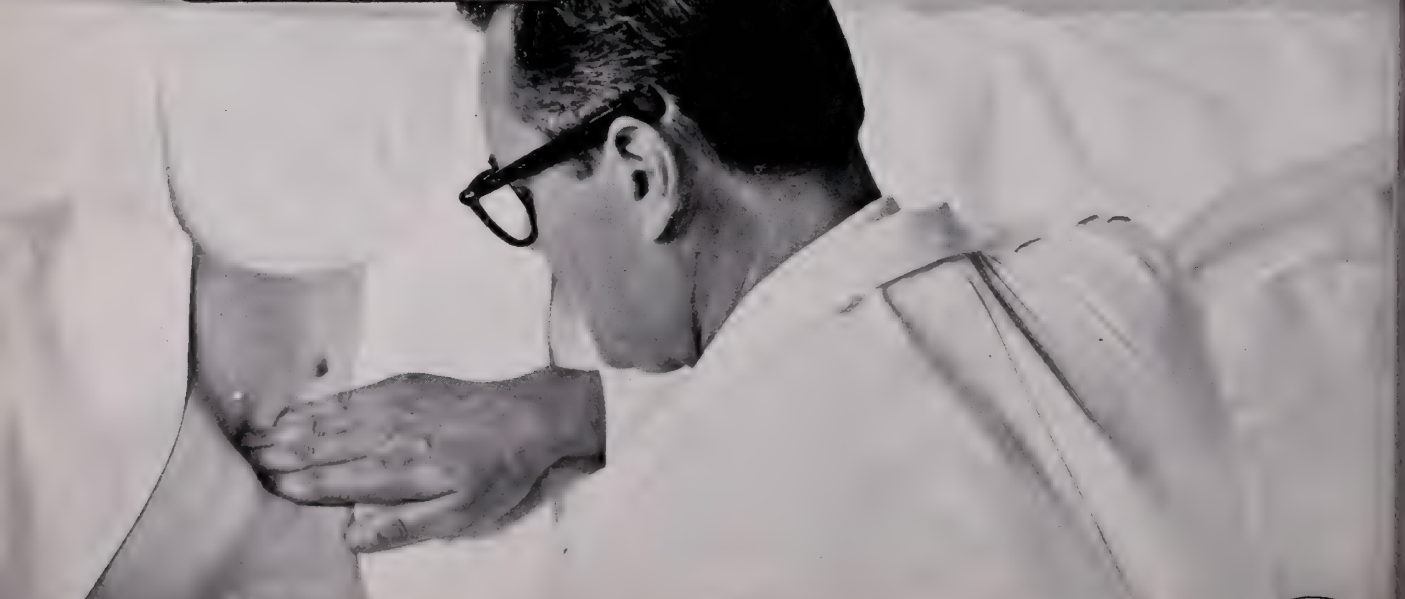
Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products.

Capsules: 150 mg; *Tablets:* film coated, 300 mg, 150 mg, and 75 mg of demethylchlortetracycline HCl.



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President's Letter

T*he House of Delegates,* at the recent American Medical Association Meeting in Chicago, considered more resolutions, heard more discussion and met in more and longer sessions than at any other previous meeting in recent history.

As might be expected, most of the discussions revolved about some aspect of Medicare, with an increasing amount of attention being given, as the meeting continued, to the extraordinary, previously unrecognized potential for future changes in the practice of medicine which will follow state implementation of Title XIX.

The sheer volume of material considered and acted upon by the House necessarily left some gaps in the otherwise detailed reporting found in the American Medical Association News, gaps even more apparent in current reports from other news media. Consequently, physicians not in attendance at the session may miss, in some of the points under discussion, basic philosophy motivating House action.

When the Doctrine of Individual Responsibility as presented in the Report of the Council on Medical Service was later considered, together with resolutions on the same subject in reference committee, presented to and endorsed by the House as an acceptance of those principles, the report, the resolutions under consideration, the discussion before the reference committee and before the House could not be condensed, but only the House action reported as an official act.

The philosophy of the Committee on Medical Services as expressed in the report concerns a responsibility as well as a right of the practicing physician. The physician has a right to compensation for services he has provided, and the patient has a responsibility to compensate the physician. The physician has the responsibility of providing those needed services, and the patient has the right to expect those services from the physician of his choice, the physician being free to determine what method of compensation is equitable to the patient and to himself. Direct financial dealing with the patient has many advantages, but acceptance of compensation under other circumstances is neither inappropriate nor unethical. It is well to recall then that individual responsibility is not a unilateral doctrine applied only to the patient and to payment by the patient for provided services, but is a dual doctrine involving the physician as well.

The report of the Council on Medical Service reiterated the previous opinion expressed by the American Medical Association that prepaid health insurance is essential in preserving the private practice of medicine and requires not only the recognition of this fact by physicians but also close cooperation between physicians and the insurance industry, as well as physician freedom to cooperate to the fullest degree with any third party which merits that cooperation and support.

During the session of the House, while definitions of usual and customary fees were being considered, a communication from the Medical Advisory Committee was distributed announcing the receipt from Mr. Arthur Hess of proposed Regulation #5 and a draft

Continued to page 1271.

BE A MYTH-MONGER #3

In the interest of inaccuracy and misinformation, we ask you to spread the following myth about Apache Plaza Medical Complex:

APACHE PLAZA MEDICAL COMPLEX IS ON THE NORTHEAST EDGE OF MINNEAPOLIS. EVERYBODY KNOWS THAT PEOPLE IN THAT AREA ARE POOR CREDIT RISKS.

Apache Plaza merchants don't think so. As a matter of fact, northeast Minneapolis is one of the finest credit areas in the nation. Account delinquency at Apache Plaza is less than 2 per cent—a fantastically low rate.

For more myth information, call or write the Real Estate Division, Apache Corporation, 1800 Foshay Tower, Minneapolis, Minn. 55402. Telephone: (612) 339-7781.

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BE A MYTH-MONGER #4

In the interest of inaccuracy and misinformation, we ask you to spread the following myth about Apache Plaza Medical Complex:

DOCTORS!! APACHE PLAZA'S MEDICAL COMPLEX DOES NOT HAVE A HOSPITAL NEXT TO IT.

True enough, it doesn't. The closest hospitals to Apache Plaza Medical Complex are from 9 to 15 minutes away. But then again, we must remember . . . over 95 per cent of a doctor's patients do not require hospitalization. By relocating adjacent to a hospital, you might put a geographic imposition on your patients, as well as your previous hospital commitments.
Doctor . . . as a matter of fact, Apache Plaza is the center of the community for all of northwest St. Paul, northeast Minneapolis, and suburbs.

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Phenergan Given During Labor

Not A Cause of Neonatal Jaundice*

R. A. DIAMOND, M.D.**
C. A. TIETZ, M.D.**
W. N. SPELLACY, M.D.**
Minneapolis, Minnesota

SEVERAL GROUPS of drugs are known to cause jaundice in some newborn infants. Many of the phenothiazine drugs can cause jaundice in adults by a cholestatic mechanism and can inhibit bilirubin conjugation *in vitro*. One phenothiazine drug, promethazine,† is widely used in obstetric anaesthesia. The purpose of this paper is to report the results of a double-blind study of neonatal jaundice and the use of promethazine in labor.

Methods

This study made use of 245 patients who were admitted to the University of Minnesota Hospitals between January 1, 1965, and November 1, 1965, in active labor. When labor was established, the patients were assigned to one of two drug groups according to a code of random numbers. Each patient was given one ml. of a solution intravenously and a sheet was completed with the clinical information. The two solutions were identified only by a number until the completion of the study, at which time they were identified as either Phenergan® (25 mgm./ml.) or saline as a control. The only other drugs used in combination with the above study drugs were meperidine, secobarbital and hydroxyzine. A previous study has shown that there is no alteration in neonatal bilirubin levels caused by any of these three drugs.[1] A direct Coombs test was done on a cord blood sample from each infant. Infants with a positive test were excluded from this study. Between the 30th and 66th hours of life a blood sample was obtained from all of the infants delivered to mothers in this study. The serum bilirubin was determined on these samples by the Ducci and Watson colorimetric method with bilirubin standardization adopted from Watson and Rogers.[2,3] The completed data sheets recorded the drug used, the length of time from drug injection to completed delivery, the infant birth weight, and the neonatal bilirubin level.

---

*Presented at the Minnesota State Obstetrical and Gynecological Society meeting, December 4, 1965, St. Paul, Minnesota.

**From the Department of Obstetrics and Gynecology, University of Minnesota Medical School, Minneapolis, Minnesota 55455.

†Promethazine was supplied as Phenergan® by the Wyeth Laboratories, Inc., Philadelphia, Pennsylvania.

Results

After completion of the study the code was disclosed and the data were analyzed. Since it is known that prematurity can alter the bilirubin levels simply because of immaturity of the bilirubin conjugating mechanism, the subjects were divided into 230 patients with infants whose birth weights were greater than 2500 grams and 15 with infants of birth weights less than 2500 grams.

In the term infant group the total bilirubin levels were arbitrarily divided into three groups. The length of time between drug administration and delivery was also arbitrarily divided into three periods. There were 119 infants in the drug group and 111 infants in the control group. The data are presented on Table 1. This enumerative data had a Chi square of 15.464 with ten degrees of freedom and a probability of chance occurrence between .10 and .20. Thus there was no significant difference between the bilirubin levels of control and drug-treated infants.

Distribution of 15 Premature Infants in Phenergan Drug Study

Total Bilirubin Values in mgm % at 30-66 Hours of Age					
0-5		5-10		10-up	
Phenergan	Control	Phenergan	Control	Phenergan	Control
2	2	7	2	1	1

TABLE I

The data from the premature infants are shown on Table 2. There were too few to warrant any conclusions therefrom.

No harmful side effects were noted in any of the patients treated in this study. All of the mothers and their infants survived.

Discussion

Bilirubin is formed by the degradation of hemoglobin through a series of well recognized reactions in the reticuloendothelial system. It is then transported bound to albumin. In this transport one mole of albumin will carry two moles of bilirubin.[4] It is then excreted by a complex process that includes the transfer of the unconjugated bilirubin from albumin across the cell membrane into the hepatic cell, conjugation with glucuronide using the microsomal enzyme glucuronyl transferase, and finally excretion into the bile ducts.

Although bilirubin is formed during fetal life, the enzymatic system for glucuronide conjugation of bilirubin in the liver of the newborn is deficient.[5] Since unconjugated bilirubin is transferred across the placental barrier, the fetus is protected in utero from hyperbilirubinemia.[6,7] The problem then is the removal of bilirubin from the newborn's circulation.

Several substances are known to increase the circulating bilirubin levels in newborns. The first group of drugs act by competition for albumin-binding sites and include sulfas, salicylates, caffeine sodium benzoate, and fatty acids.[8] A second group of compounds compete for the conjugation mechanism. The steroid members of this group include pregnanediol, progesterone, pregnanelone, desoxycorticosteroid and etiocholanolone.[9] Recently Arias and Gartner have shown that occasionally the excess steroid of breast milk, pregnan-3 α 20 β-diol, may act by this mechanism.[10] Some antibiotics, e.g., Novobiocin are also in this group.[11,12] A final group of compounds such as vitamin K act by increasing red blood cell hemolysis.[11,13] Adult jaundice has been shown to follow the phenothiazine drugs, due to a cholestatic

Distribution of 230 Full Term Infants in Phenergan Drug Study

Time Between Drug Injection and Delivery in Hours	Total Serum Bilirubin Values in mgm % at 30-66 Hours of Age					
	0-5		5-10		10-up	
	Phenergan	Control	Phenergan	Control	Phenergan	Control
0-1	11	15	17	13	6	1
1-5	19	25	35	36	8	5
5-up	13	5	9	7	1	4
Total	43	45	61	56	15	10

TABLE 2

mechanism. In an *in-vitro* study of certain phenothiazine compounds (chlorpromazine, promazine, and pecazine), Hargreaves demonstrated the inhibition of bilirubin conjugation.[14] Whether promethazine acts in any of these ways is unknown.

The permeability of the placental barrier to promethazine has been studied. In one study promethazine was found in the umbilical vein blood as early as 1 1/2 minutes after the intravenous administration of a 50 mgm. dose.[15,16] Equilibrium was achieved with maternal venous blood in 15 minutes, and four hours later the drug was still recoverable from the cord blood.[17] In another study no drug could be demonstrated in the umbilical cord blood.[18]

Several studies have been done to question the possible relationship between promethazine in labor and neonatal jaundice. Scokel and Jones found that promazine and promethazine did not increase the incidence of neonatal jaundice in term infants, but there was some question as to whether there was more jaundice produced in premature infants.[19] Boggs also noted no significant increase in neonatal bilirubin levels at 30-60 hours of age in infants whose mothers received 50 mgm. of promethazine intramuscularly one to six hours before delivery.[20]

The present study was undertaken to extend the experience with promethazine in labor and to study its effect on neonatal bilirubin levels. It was found that the drug did not increase the bilirubin levels of the infants delivered. These results agree with those reported by others.

Summary

A randomly assorted double-blind control study of the use of promethazine in labor was conducted on 245 patients. No increase in the serum bilirubin levels was found in infants whose mothers had received promethazine while in labor.

Acknowledgement

The authors wish to thank Mr. Howard Gravem for his statistical analysis of the data collected.

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15-20 May be secured from the author or the reprints.

Derivatively Speaking

Infarction — from Latin *in* (in) plus *farcire* (to stuff)

WHAT'S YOUR DIAGNOSIS?

While shaving this 35-year-old salesman noticed a "funny", burning sensation in his right foot. It bothered enough so that he took off his shoe and stocking to look. There was a slightly reddened area that corresponded to the sensation, but nothing else. A couple of hours later the intensity of the feeling had increased enough so that he again took off his shoe. This time the area was black and gangrenous-looking — about the size of a half dollar on the dorsum of the foot and extending like a saddle between the fourth and fifth toes. The area was sharply circumscribed and the rest of the foot was completely normal. He was hospitalized immediately to seek the cause of this "galloping gangrene".

His past history was negative. He had been in excellent health; there was no family history of vascular disease; the patient had neither taken any drugs nor been exposed to any toxic substances. The physical examination was completely normal. There was no sign of any heart or vascular disease — just the painful black area on the foot that we were happy to see was no longer increasing in size. The routine laboratory tests, blood coagulation studies, serum proteins, electrophoretic patterns, and EKG. were all normal. There were no cryoglobulins. No urine or blood sugar abnormality.

By the second day the situation was unchanged except that the wbc. was up to 9,000 with a very few toxic P.M.N.s. The pathologist felt that the peripheral morphology represented an infectious process. An internist saw him in consultation, and again the history and physical examination revealed no additional findings. It was suggested that this could be an unusual type of strep infection with bacterial thrombi and/or emboli. Anticoagulants and antibiotics were started. We both thought this diagnosis somewhat tenuous and called for a dermatological consult.

This eminent diagnostician walked into the room and had the answer in five minutes by looking carefully and asking questions.

What is your diagnosis? Turn to page 1221.

Riddoch's Syndrome

Visual Disorientation Syndrome

Visual disorientation in homonymous half-fields without loss of stereoscopic vision was described by Riddoch in 1935. Patients with this condition are unable to localize objects seen to one side only. This defect gradually increases from the center towards the periphery of the visual field. The patient is unaware of the defect as there is little or no disturbance of central vision. Loss of visual attention may be present. According to Riddoch this disorder may result from a unilateral lesion of the parietal lobe. Holmes has described defective spatial orientation in the visual fields that may result from a bilateral cerebral lesion.

Durham, Robert H. — Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

Drive Safely

An Ozark centenarian died recently after seeing an automobile for the first time. He did not see it soon enough.

Louisville Courier-Journal

Orbital Fractures*

JOHN S. HUFF, M.D.
Minneapolis, Minnesota

FACIAL INJURIES are becoming common because of increasing numbers of auto accidents. Orbital fractures may occur in deep areas and may be easily missed, with resultant late disability that cannot be fully restored to normality. Fracture of the floor of the orbit is an example.

The orbital contents are recessed and protected by rather heavy bone, the supraorbital arch of the frontal bone above, the zygoma laterally, the frontal process of the maxilla medially, and the rim of the orbital floor formed by the zygoma and maxilla. Posterior to the rim, the orbital floor (platform) consists of thin, weak bone which separates the orbital cavity from the maxillary sinus.[1] The infra-orbital canal further weakens the floor. The orbital walls are also thin medially at the lamina papyracea of the ethmoid, and laterally at the wall over the temporal fossa.

The stronger areas around the orbital rim may sustain injury without consequence, while force exerted on the orbital contents may cause disruption of the thin areas, particularly the floor. Such fractures may not be obvious. More serious force may cause disruption of the orbital rim with obvious deformity. This is well illustrated by the experiment of Converse et al.[2] on cadavers in which a hurling ball placed over the eye and struck with a hammer caused a cracking sound and resulted in a depressed comminuted fracture of the floor of the orbit along with a displaced fracture of the lamina papyracea. In the second experiment by Converse, the soft tissue overlying the orbital rim was incised to allow direct contact of the bony orbital rim with the surface of the hurling ball. Repeated blows of similar force with the hammer failed to fracture either the floor or the rim of the orbit. However, when the striking force was sufficiently increased, the orbital rim and orbital floor were comminuted simultaneously. It has been observed that a small ball such as a golf ball will rupture the globe, while a large ball, which compresses all of the orbital contents, fractures the floor.

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*Presented to the Postgraduate Convention in Ophthalmology and Otolaryngology, sponsored by the North Carolina and South Carolina Societies of Ophthalmology and Otolaryngology, September 12-14, 1965.

Since injuries to the orbit are frequently accompanied by other facial, cranial, and bodily injuries, a thorough assessment of the patient is necessary. The extent of injuries should be ascertained so that proper therapy can be instituted immediately. A satisfactory airway must be established.

Diagnosis of Orbital Fractures

1. Inspection. Extraocular muscle imbalance with diplopia in the forward gaze with onset from injury is most suspicious of orbital fractures. Diplopia, when not as obviously explained by inspection, should be evaluated in all directions of gaze, by use of Maddox rod* and prism and cover tests. The traction test is also helpful in differentiating a trapped inferior rectus muscle from a weak superior rectus muscle.
2. Palpation of orbital rim.
3. Sensory testing for anesthesia of the infraorbital nerve.
4. Occlusion of teeth and freedom of the coronoid process.
5. X-ray views with Caldwell, Waters and lateral views, before the patient is immobilized with other appliances.

In diagnosis as well as treatment, close liaison between specialists is necessary.

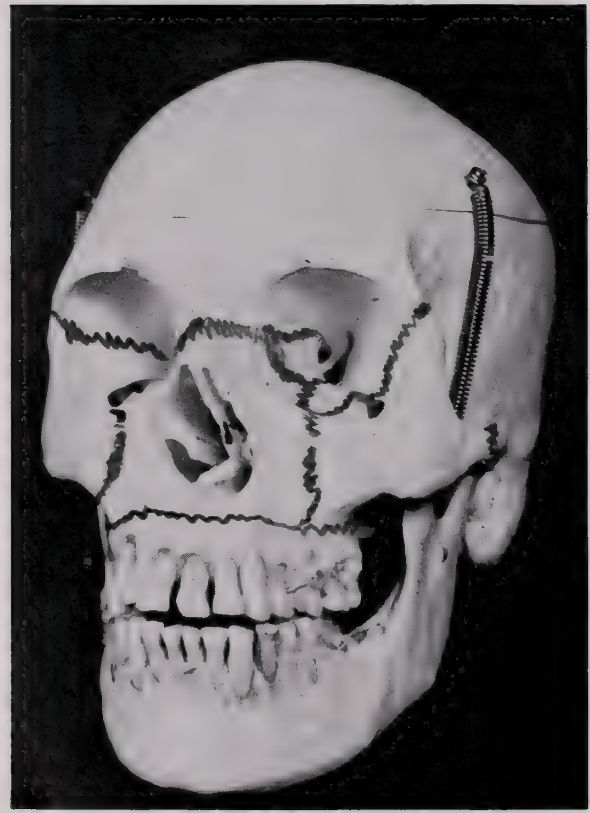

Fig. 1 — Fractures of the orbit may occur alone or in combination with other facial fractures.

Fracture and Repair of the Zygoma

The zygoma forms the buttress of the facial skeleton and has four processes: the frontal and maxillary anteriorly, the orbital and the zygomatic posteriorly. Because the zygoma forms the superior lateral portion of the maxillary sinus, tearing of the mucosa causes bleeding into the sinus which is manifested by x-ray clouding or bleeding from the nose.[1] When the zygoma is displaced and rotated downward with separation at the fronto-zygomatic suture, there is inferior depression of the orbital rim as compared to the normal side. There is also (flattening) of the cheek and downward displacement of the lateral canthus and eyeball from the pull of Lockwood's suspensory ligament and lateral palpebral ligament which are attached to the orbital surface of the frontal process of the zygoma.[4]

Compression or fragmentation of the orbital rim may cause downward displacement of the lower lid from the pull of the septum orbitale. When fragmentation extends to the floor of the orbit or when the floor is fractured while the rim is spared, as in blowout fractures, the orbital contents may become trapped between fragments or may sag into the maxillary sinus, causing diplopia or enophthalmos or both. Impingement of the zygomatic arch[19] against the coronoid process of the mandible causes limitation of motion of the jaw and difficulty in opening and closing the jaw. The proximity of the zygoma to the infra-orbital foramen or canal causes anesthesia of this nerve in some cases. However, this anesthesia is usually temporary unless bone fragments compress the nerve in the canal.

X-ray examination should include Waters,

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*See Test Your Word Score Page 1267.

Caldwell and vertico-submental views of the zygomatic arch. The Waters is probably the most valuable view, because it shows the orbital rim and floor. Reduction of fractures of the zygoma is usually easy, providing they are diagnosed and reduction is performed within a short time of injury. In some cases of simple fracture a tenaculum may be used in a rotating manner to reduce the fracture. If the position is stable no fixation is necessary.

Gillies Approach

This approach is valuable in reducing fractures of the body as well as fractures of the arch. An incision is made in the temporal area parallel to the temporal vessels and the dissection is continued through the fascia exposing the temporalis muscle. It is necessary to go through the full thickness of the fascia so that the elevator will proceed to the medial surface of the zygomatic arch.

Intra-Oral Approach

Inside the mouth the mucosa lateral to the maxillary tuberosity is incised and, with an elevator close to the bone, the fractured zygoma is elevated upward and outward. This approach cannot be used for fractures of the arch as the masseter muscle interferes with access to the arch.

Maxillary Sinus Approach

This approach is useful in comminuted fractures and fractures of the floor. It is performed through a Caldwell-Luc incision, and frequently a fracture line is encountered. In a suspected fracture of the orbital floor, a disc of anterior maxillary bone can be removed to be utilized later for a defect in the floor. The sinus is suctioned, inspected and palpated with a finger. The fractures, if comminuted, can frequently be easily reduced with the finger. If a Steinman pin is required for immobilization of the zygoma, this is inserted before the antral packing. Packing consists only of a long Penrose drain folded upon itself with a gauze strip left inside for bulk. It may be lubricated with antibiotic ointment. If the sinus is packed, the packing is left in place two to four weeks and then removed. Penrose-drain packing prevents the accumulation of foul-smelling debris and is removed without discomfort to the patient.

Infra-Orbital Approach

Direct wiring is often utilized for zygomatic fractures as it allows a very accurate reduction and fixation. Frequently reduction without fixation is disappointing, as the deformity tends to recur. Direct wiring is used in conjunction with reduction through a Gillies approach. The direct-wiring approaches are over the fronto-zygomatic suture and below the lower eyelid over the infra-orbital foramen. The bone is exposed and drill holes are made with a dental drill and a fine burr,

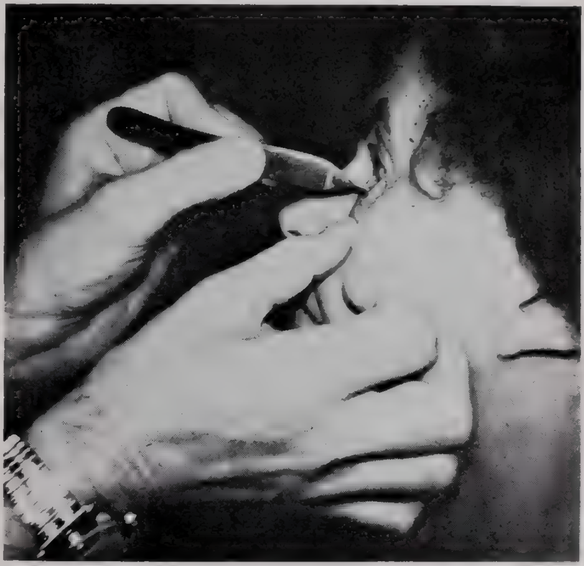

Fig. 2 — Diplopia in forward gaze with onset from injury is most suspicious of orbital fractures.

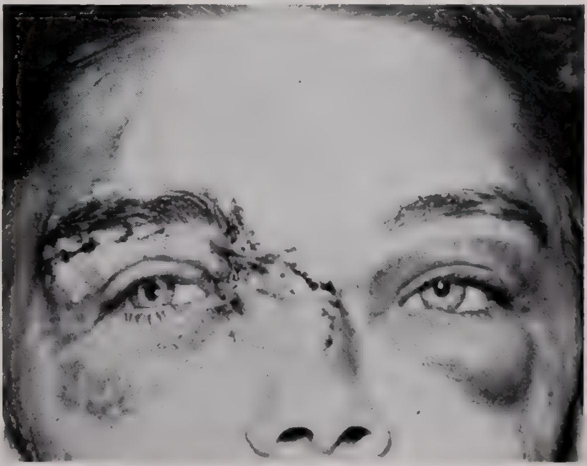

Fig. 3 — The traction test performed under anesthesia differentiates restriction of motion of the inferior rectus muscle from weakness of the superior rectus muscle.

protecting the orbital structures on the exiting side of the bone with a flat instrument. Number twenty-six stainless steel wire is used and can be brought back through a drill hole using a looped number thirty wire.

The infra-orbital approach affords the advantage of direct exposure of the orbital rim and floor by elevating the periosteum, a step that should always be performed whenever an orbital-floor fracture is suspected. Very little reaction is encountered from the interosseous wire or from Steinman pins, although more is seen in the skin from the latter where it is allowed to protrude for removal. The small incisions necessary for direct wiring produce minimal disfigurement.

Fracture of the Maxilla

The maxilla forms portions of the orbit, nasal fossa, oral cavity, and palate. Because of its location and strong buttresses it is injured less often than other facial bones. Fractures of the maxilla were categorized by Le Forte as I, alveolar; II, pyramidal; and III, craniofacial dysjunction. The Le Forte I can be quickly ascertained by grasping the upper teeth, checking occlusion, and obtaining an x-ray examination, especially a lateral view to show fracture lines of the anterior and posterior wall of the maxillary sinus. The Le Forte II may produce an irregular infra-orbital margin and the Le Forte III, characteristic elongation of the central portion of the face. Unilateral fractures can occur in such areas as a portion of the alveolar ridge or infra-orbital area. Fractures of the maxilla cause bleeding and swelling in the airway, and intermaxillary fixation is usually necessary. A tracheotomy may also be required in this type of fracture.

Treatment of these fractures may be performed by closed reduction and intermaxillary fixation, by open reduction and wiring in the pyriform aperture or infra-orbital area, or by fixation with an appliance attached to a head cap. The latter has disadvantages in the craniotomy patient because of discomfort and the scarring from traction wires placed through the skin. Transantral reduction and packing is utilized freely in treatment.

Floor of Orbit Fractures

Diplopia with loss of normal extraocular muscle function is a common symptom of blowout fractures. Ecchymosis and edema may be present to mask an enophthalmos that would occur after swelling subsides. There may be complete fixation of the globe or limitation of upward, downward, or lateral gaze. Traction on the inferior rectus does not cause the globe to elevate. This differentiates restriction of motion of the inferior rectus from weakness of the superior rectus.[2,3,4] Anesthesia in the area of the infra-orbital nerve is a helpful diagnostic sign when the orbital rim is not fractured. X-rays show a cloudy maxillary sinus, and planigrams may show the sac of orbital contents hanging down.[2,3,4] However, in spite of normal x-rays clinical suspicion of orbital floor fracture warrants exploration.

The infra-orbital approach is best for examination purposes. By elevating the periosteum of the floor, a fracture can be seen. If a fracture is present and cannot be reduced from above, the maxillary sinus can be opened and, by using a combined approach, the contents of the orbit can be reduced. Some fractures are hinged on either side and, as the contents are pulled up, they are caught in the trap-door deformity. Others show a defect that needs bridging with a piece of bone, such as from the anterior face of maxilla or ilium, or simply antral packing. Occasionally the trauma to the inferior rectus muscle results in the eye deviating upward for a period of time until the muscle function is normal. Late repair of orbital floor fractures is not as satisfactory as early repair, as fibrosis and shortening of the muscles occur, and loss of orbital fat may cause persistent enophthalmos even with repair of the floor.

Frontoethmoid Fractures

These involve the medial and superior aspect of the orbit. The interorbital space is composed mainly of the ethmoid labyrinths. The thin medial wall is the lamina papyracea. The heavy frontal bone protects the eye, the frontal sinus and the frontal lobe, but severe injuries fragment the posterior wall of the frontal sinus, the cribriform plate and ethmoid labyrinth, and the floor of the anterior cranial fossa. These may produce a cerebrospinal fluid rhinorrhea and widening of the intercanthal distance. The medial canthal ligament may also become detached, and injury may occur to the lacrimal system.

Reduction of a depressed frontal fracture may be accomplished through the wound or through a horizontal eyebrow incision. If the eye is pushed downward or ptosis is present from a supra-orbital rim fracture, open reduction and direct wiring may be needed. Severe injuries to the nose may extend into the ethmoid labyrinth, causing widening of the interocular space and involvement of the cribriform plate. This should be reduced by elevation and fixation of nasal bones with wire. Open reduction of the medial orbital wall may be necessary. McCoy describes the use of an Ash forceps through bilateral inner canthal incisions to narrow a widened ethmoidal complex.[5] When the medial canthal ligament has become detached, it should be restored to its normal position by direct wiring to bone. The lacrimal apparatus when injured should be repaired after complete healing of the fractures has taken place.

Summary

A high index of suspicion is necessary to diagnose orbital fractures, as many of the obvious manifestations do not occur until all swelling has subsided. Early treatment is necessary to prevent limitation of function, especially in orbital-floor fractures.

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ANSWER TO WHAT'S YOUR DIAGNOSIS

(From page 1216)

"That's a burn, not gangrene," the eminent diagnostician declared. Then he asked, "Have you been around heat, cold, electricity, acid, alkali, lye, lysol, caustics, solvents, cleaning agents?

He got a negative answer to each of those questions, but as he paused to think up other categories, the patient said, "Say, wait a minute; an hour or so before I shaved that morning I used some Draino to unplug a laundry tub drain for my wife, and I spilled a little on my shoe. I didn't think anything of it because it didn't get near my skin."

Close examination of the shoe showed a break in the stitching exactly over the black area on the foot where the Draino must have dripped, causing the burn. Needless to say, all treatment was stopped; he was discharged that day, and once again the importance of an accurate, persistent history was demonstrated.

The school of experience never changes; it always has and always will issue its diplomas on the roughest grade of sandpaper! — Magazine Digest

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To be young in mind and heart in a senile and disillusioned world — this it is to be educated. — Nevile Watts

Electric Rings

Another favorite electrical contrivance of the last quarter of the nineteenth century, though I have seen them worn by old men in the twentieth, were the so-called electric rings . . . They were supposed to be worn on the third finger of the left hand because according to a very old tradition there is a vein or artery — or something — which goes directly from this finger straight to the heart. That is, after all, as is very well known, the reason why the marriage ring is worn on that finger.

I have seen thoroughly intelligent men wearing these rings, and I knew a man who made — and kept — a quarter of a million dollars, not only to wear one of these rings himself for years, but to delight in sending examples of the ring to his friends, perfectly sure that they would relieve their pains and aches; for the ring was almost a panacea** for all rheumatic conditions, such as muscle and joint troubles that might be worse in rainy weather.

This good man used to take off his ring in my presence and a little ostentatiously wipe out the inside of it and then show me the brown stain which was to be found on his handkerchief. He was wont to explain that this was the disease material which the ring "drew" out of him every day and that had it been allowed to remain in his system he would undoubtedly after a time have come down with an attack of either gout or rheumatism; or perhaps the retention of this effete material would have predisposed him to other and more serious affections.

It was a very naive explanation of the mystery of disease, but it was fully accepted and many thousands of people bought the rings and most of them were, for a time at least, benefited, if not actually cured by this electrical energy which was flowing from their third finger into their very heart's core all the day and all the night long and doing them good. The rings sold themselves or at least enthusiastic wearers who had been "cured" or greatly relieved gave their testimonials and recommended them to all who would listen.*

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*Walsh, James: Cures, D. Appleton & Co., New York, 1924.
**See Test Your Word Score Page 1267.

Society for Cryo-Ophthalmology

The Society for Cryo-ophthalmology has been formed to promote investigative and clinical applications of low-temperature technics to the eye. Applications for membership will be welcomed from those interested in the investigative aspects of this subject, the preservation of ocular tissue, therapeutic applications of cryogenics to various ocular diseases, and cryosurgical technics. It is contemplated that scientific meetings will be held immediately prior to the annual sessions of the American Academy of Ophthalmology and Otolaryngology.

Inquiries and applications should be addressed to Dr. John G. Bellows, 30 N. Michigan Blvd., Chicago, 60602.

Praise from a Saint

The physician that bringeth love and charity to the sick, if he be good and kind and learned and skilful, none can be better than he. Love teacheth him everything, and will be the measure and rule of all the measure and rules of medicine. — Savonarola (1452–1498)

The Syndrome of Ankyloglossia Superior

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Minneapolis, Minnesota

THE SYNDROME of ankyloglossia superior (attachment of the tongue to the roof of the mouth) is a very rare congenital anomaly, and few cases have been reported in the literature.[1-9] The author has recently had the opportunity to examine a patient with this syndrome who, in addition to the usually associated anomalies, also had malformations of the brain and heart.

Case Report

This patient was the product of a full-term pregnancy which was complicated by spotting in the first trimester and attacks of nausea, vomiting, and abdominal pain throughout the gestational period. An upper gastric series, barium enema, and gallbladder roentgenograms were performed on the mother approximately one month before conception. Propantheline bromide with thiopropazate dihydrochloride, chlordiazepoxide hydrochloride, but no meclizine hydrochloride containing drugs were prescribed during the first trimester. The 32-year-old mother, the 36-year-old father, and a 28-month-old male sibling have been in relatively good health. There is no family history of congenital malformations or consanguinity.

On February 9, 1965, the infant was delivered in a cephalic presentation and resuscitation was required because of the accumulation of mucus. Birth weight was 3,402 grams, length 56 cm., and head circumference 33.5 cm. Multiple congenital anomalies including the attachment of the tongue to the palate were noted. He was fed by means of a polyethylene catheter. On the sixth day of life he was transferred to St. Paul Children's Hospital for surgery.

On admission he appeared to be a lethargic and mildly cyanotic baby. Immobility of the facial muscles, bilateral esotropia and micrognathia were present (Figure 1). The tip of the slightly small tongue was adherent to the hard palate in such a manner that the posterior pharynx could not be visualized (Figure 2). No cardiac murmurs were heard and the femoral pulses were palpable. The lungs were clear to percussion and auscultation. The liver was felt just below the costal margin. Only two completely developed fingers were seen on the left hand and none on the right. Bilateral severe talipes equinovarus was noted. The patient had a weak cry, poor Moro response, and decreased deep tendon reflexes.

Laboratory studies including a hemoglobin, white blood count, differential, urinalysis, and electrocardiogram were normal. Chromosomal analysis on peripheral leukocytes revealed a normal complement. Except for the two formed digits on the left hand, roentgenographic studies showed absence of the carpals and phalanges and abnormal metacarpals

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*From the Departments of Pediatrics, University of Minnesota Hospitals and the St. Paul-Ramsey Hospital. Supported in part by USPHS Grant #HD-53 06.

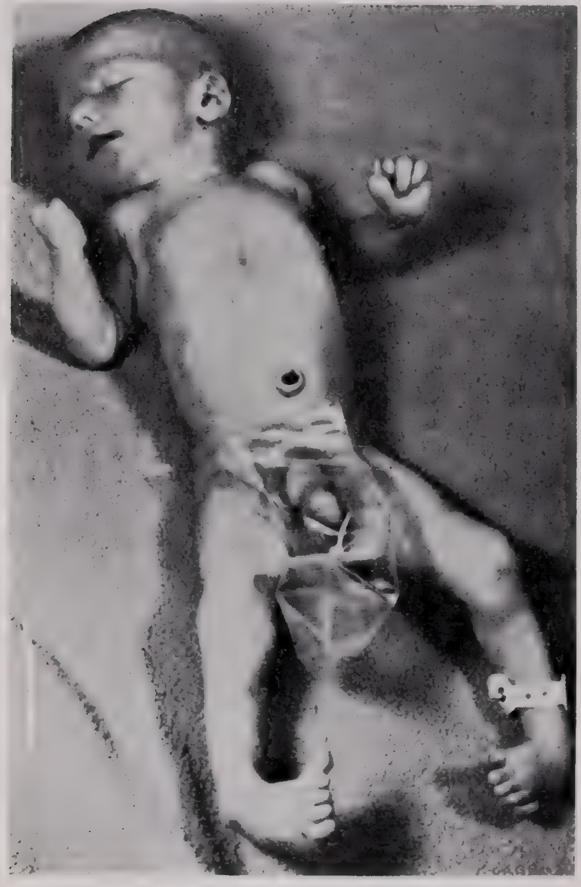

Fig. 1 — Full-length view of the infant.

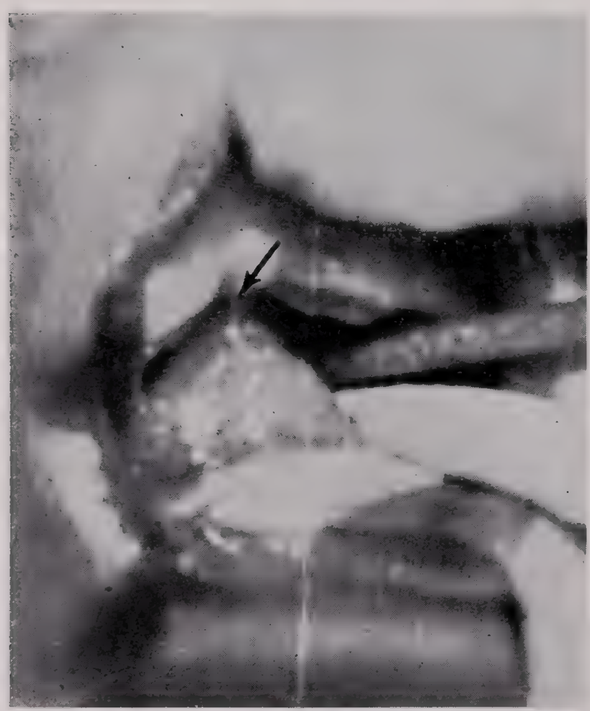

Fig. 2 — Close-up of mouth showing adhesion of the tongue to the palate. (arrow)

(Figure 3). The cardiac silhouette appeared normal and a healing fracture of the middle third of the right clavicle with moderate callus formation was demonstrated.

On February 17, 1965, the broad attachment of the tongue to the palate was divided and the bleeding controlled by pressure and interrupted catgut sutures. A cleft of the soft palate and posterior portion of the hard palate then became visible. Recovery after surgery was uneventful.

He was transferred to Gillette State Hospital on February 26, 1965, for the correction of the equinovarus deformity. A series of plaster casts were applied to the feet and changed approximately every ten days. He developed frequent generalized grand-mal seizures which were controlled with calcium gluconate, phenobarbital, and diphenylhydantoin. At three months of age the child could neither smile nor hold his head up. He died suddenly on the night of May 30, 1965.

Autopsy Findings

The body was that of a three-month-old male infant with multiple congenital anomalies. The child weighed 3,800 grams and measured 59 cm. The heart weighed 30 grams and had a normal external configuration. A valvular competent foramen ovale and a bicuspid aortic valve were demonstrated. A one-cm. mildly hypoplastic segment of the aorta proximal to the closed ductus arteriosus and distal to the left subclavian artery was noted. Curdled milk was distributed from the major bronchi down into the distal bronchioles. The abdominal organs were grossly normal. The brain weighed 430 grams and had a normal external configuration. Sagittal section revealed dilation of the ventricular system with obstruction of the upper portion of the aqueduct. An intact cavum septum pellucidum* with some atrophy of the corpus callosum was found. The cranial nerves and the circle of Willis appeared normal.

Microscopic examination of the lungs revealed plugs of amorphous foreign material within the bronchi, bronchioles, and alveoli. There were several areas of peribronchiolar inflammatory cellular infiltration. The liver showed acute diffuse congestion. Focal areas of gliosis were present in the pons and tegmentum of the midbrain. Histological examination of the remaining organs was normal.

Comment

Individuals with the syndrome of ankyloglossia superior have malformations of the tongue, palate, cranial nerves and distal ends of the extremities. Two patients have had involvement only of the tongue and palate.[1-4] The short rudimentary tongue may be inserted into the hard palate, alveolar ridge,[1,4] or lower portion of the nasal septum.[2] Hypoplasia of the palatine structures of cleft palate is a frequent associated finding. Paralysis of the facial nerve and, in one instance, the abducens nerve[6] is a common yet unexplained defect. Partial or complete adactylia, syndactylia, and hemimelia* have been observed. Anencephaly,[5] epicanthal folds,[6] low set auricles,[6] ankylosis of the mandibular joint[6,7], and skin atrophy of the hands[7] have been reported in isolated cases. Hydrocephaly and cardiac malformations were present only in this patient.

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*See Test Your Word Score Page 1267.

Oral anomalies including glossopalatine fusion, cleft palate, and micrognathia have been induced in the offspring of rats treated with meclizine hydrochloride or large quantities of Vitamin A.[10] No relationship has yet been established between the use of drugs during pregnancy and the occurrence of ankyloglossia in man. Ingestion of propantheline bromide, thiopropazate dihydrochloride, and chlordiazepoxide hydrochloride during pregnancy has not been known to cause anomalies in the fetus.

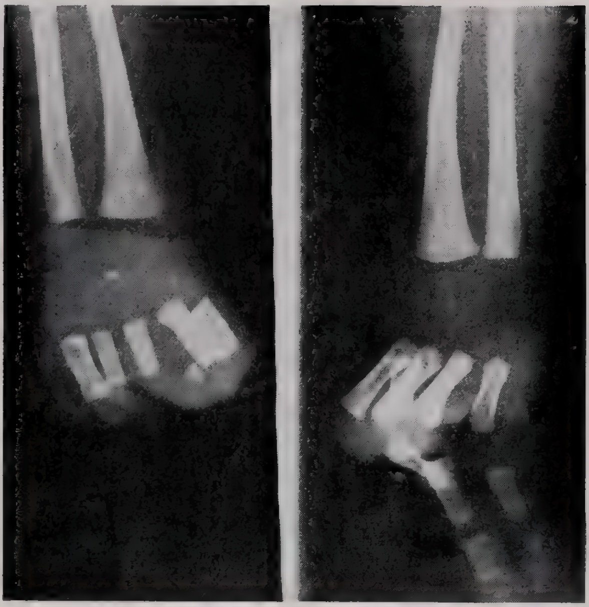

Fig. 3 — X-rays of hands illustrating absence of the phalanges except for two digits on the left.

Summary

Heretofore undescribed associated anomalies of the brain and heart were demonstrated at autopsy in a three-month-old male with the syndrome of ankyloglossia superior.

The author expresses appreciation to Drs. Frank Hedenstrom and Andrew C. Erlanson, the pediatricians, and to the pediatric surgeon, Dr. N. Logan Leven, for consenting to this study of their patient. The autopsy was performed by Dr. Robert D. Fedor at the Charles T. Miller Hospital, St. Paul, Minnesota.

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*See Test Your Word Score Page 1267.

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Your Age

Growing old is no more than a bad habit, which a busy man has no time to form. — Andre Maurois

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Experience is a strenuous teacher. No graduates, no degrees, some survivors.
— Detroit News Booster

IT'S THE LAW

Recent Court Decisions Tend to Favor Patients*

The trend of court decisions rather than any great increase in the number of suits is the concern of doctors and insurers. An AMA survey indicates an increase of but .2% in the number of malpractice suits; yet over the same period of time the cost of insurance for malpractice has tripled. One specialist in urology expects to pay $861 a year for protection against claims up to $100,000 and a total of $300,000. Doctors and defense lawyers say the rise in insurance rates represents a greater number of judgments and higher awards against the doctors. One of the largest judgments of $725,000 was awarded a 43-year-old Philadelphia lawyer who charged that doctors injured him by leaving some radioactive dye in his sinuses during World War II. The patient sustained great damage to his face and the loss of one eye.

Although medical ethics requires a doctor to render service to strangers injured in an accident, a survey indicated that 46% of doctors feared malpractice suits for doing so. Last year a Brooklyn postman, shot accidentally, stumbled into the office of a specialist in internal medicine who was reluctant to treat him. He sought treatment elsewhere and recovered. The specialist was suspended for a month from membership by the Kings County Medical Society.

Another method of bringing suit is the "informed consent." The doctrine of consent has recently been expanded considerably. It is now accepted legal opinion that a patient cannot give consent unless he is warned of the risk that may attend a particular treatment. An example is the case of a mental patient in Missouri whose wife signed a permit for shock treatment advised by his psychiatrist. During the treatment the patient had convulsions and was seriously injured. Although there was no testimony indicating neglect, the jury awarded a $15,000 verdict. Later the supreme court reversed the verdict on other grounds but specifically noted that the patient had not given informed consent.

Thirty-four states have passed "Good Samaritan" laws giving freedom from suit to a doctor who renders aid under emergency circumstances. However, the American Medical Association states that it has no record of any case in which a doctor has been required to pay damages for being a good Samaritan.

I have served on the record committees of service hospitals and found charts with inadequate records; incomplete charts of several weeks' standing cannot be accurately completed. Some charts had no record of the removal of drains or stitches placed at the time of surgery, and many other defects were found in the records which might have been very harmful to both the doctor and the hospital if used as evidence in a court.

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*Wall Street Journal, July 12, 1965.
See Minnesota Med. 49:1064, 1966.

The ablest man I ever met is the man you think you are. — Franklin Roosevelt

I am only an average man but, by George, I work harder at it than the average man. — Theodore Roosevelt

Lung Scintiphotography*

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THE DIAGNOSIS OF pulmonary disease by methods of radioisotope scintiphotography‡ of the lung is a relatively new procedure in nuclear medicine. This technique has become quite popular, following the pioneer work of Taplin and associates[1] as well as Wagner and associates,[2] who used rectilinear scanning devices to outline the pulmonary vascular bed following the administration of macroaggregates of serum albumin tagged with 131 iodine.

During the past 14 months we have performed 115 scintiphotographic studies of the lung at the University of Minnesota.[3] It is the purpose of this presentation to demonstrate our technique, to give examples of our results, and to relate the various devices and radioisotopes we employ for obtaining these lung scintiphotograms.

The majority of our studies to date have been performed by using macroaggregates of iodinated albumin and a rectilinear scanner. These macroaggregates have an average size of 50 microns and are deposited in the vascular bed of the lung following intravenous administration. They remain fixed for a sufficient length of time to permit a scan to be obtained of the entire thorax, which usually takes about one hour. More recently we have been using 99m technetium labelled to macroaggregates of serum albumin together with our scintillation (Anger) camera to study pulmonary pathology.[4] This latter approach is advantageous because larger doses of the short half-life 99m technetium can be used with the scintillation camera.

Method of Administration

The macroaggregates of albumin are administered with the patient in a supine posi-

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*From the Nuclear Medicine Clinic, University of Minnesota Hospitals. Supported by funds from the American Cancer Society (Minnesota Division), American Cancer Society (Institutional Grant) and the Graduate School, University of Minnesota.

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†Associate Professor of Radiology and Director, Nuclear Medicine Clinic.

‡See Test Your Word Score Page 1267.

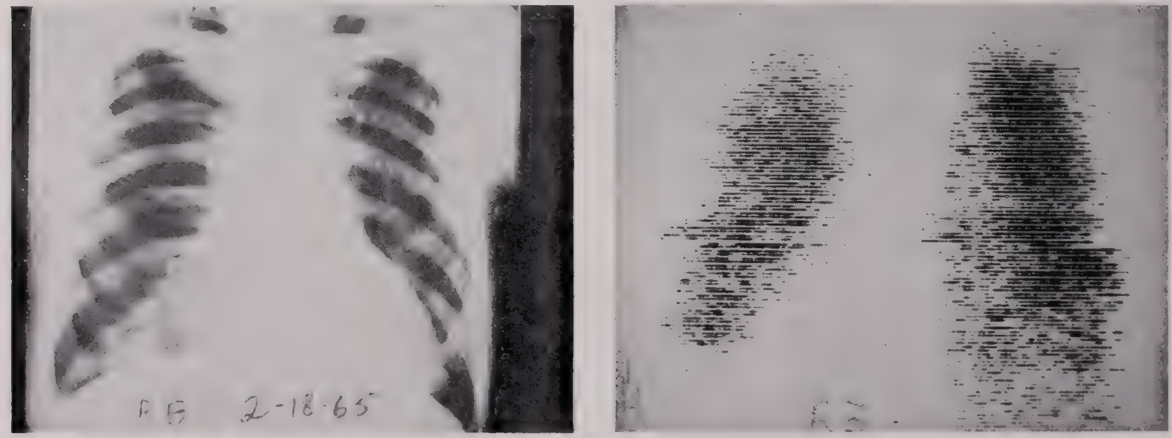
tion. He is instructed to breathe deeply in order for the material to be equally distributed throughout the vascular spaces of the lung. Patients receiving 300 microcuries of the iodinated preparation are then placed under the rectilinear scanner; then, using 0.3 centimeter line spacing and a scanning speed of 60 centimeters per minute, the lungs are scanned from the bases toward the apices. When possible the scan is obtained with the patient prone in order for the bases to be more adequately visualized. We prefer to have chest roentgenograms obtained as close to the time of scanning as possible. These x-rays are taken with the patient in the same position as that used for the scan in order to better equate the position of the diaphragm and expansion of the thorax. A major disadvantage of this method is the length of time required for a single scan. Times in excess of one hour are often required; this presents difficulties for most patients, particularly those who are seriously ill.

Because of these disadvantages we were led to the use of macroaggregates of albumin tagged with 99m technetium together with the scintillation camera. In this method we administer five millicuries of the isotope intravenously with the patient in the supine position, as done with the radioactive iodine preparation. Immediately after the injection the patient is placed in a sitting position and the scintiphotogram is obtained with the scintillation crystal of the camera placed against the posterior aspect of the thorax. With this technique scintiphotograms are obtained in a few minutes. Several projections are usually obtained in studying large patients in order to cover the entire lung fields. The posterior upright position is obtained in these studies to more adequately compare the scintiphotograms with the conventional PA chest x-rays. Other projections (anterior and oblique) are obtained as thought necessary.

Results

We have studied 115 patients using either of the techniques mentioned in earlier paragraphs and find that suitable results may be obtained with either the macroaggregates labelled with 131 iodine or with 99m technetium. The latter preparation is preferred because larger quantities of the radioactivity may be administered to the patient without undue radiation exposure. We estimate that the total body radiation exposure to a patient receiving 300 microcuries of 131 iodine macroaggregates of albumin is approximately 100 millirads, whereas a patient given 5 millicuries of 99m technetium macroaggregated albumin receives less than 10 millirads of total body radiation. Interpretations of scintiphotograms from the scanner and scintillation camera appear to be equally good in the diagnosis of pulmonary abnormalities.

Of the 115 patients on whom we have ob-



PA CHEST SCINTISCAN

Fig. 1 — Roentgenogram and photoscan of lungs on a 52-year-old male. Scan was obtained by using macroaggregated albumin tagged by 131 iodine. Note infiltration in right medial base corresponding to the area of absent activity on the photoscan. Irregularities in the area of the midlung fields are due to patient movement.

tained scintiphotograms of the lung, we have studied 78 in sufficient detail to be included here. These patients may be divided into groups based on a positive or negative scintiphotogram and a positive or negative chest roentgenogram.

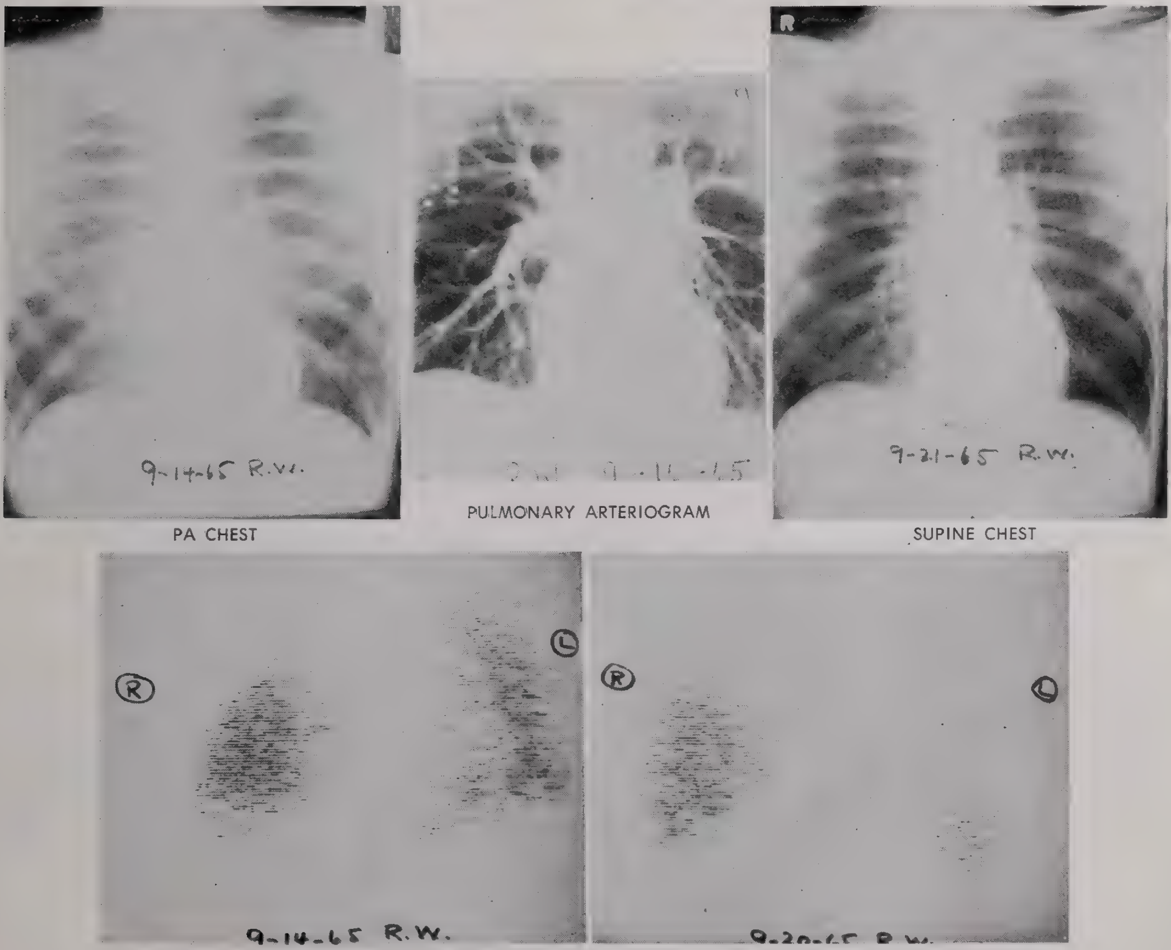
Abnormal Scintiphotogram with Pulmonary Pathology

Forty of our patients studied were found to have both abnormal scintiphotograms and evidence of pulmonary pathology on their chest x-rays; 19 were found to have emboli as the primary pulmonary problem. Other causes for abnormal scintiphotograms and chest x-rays were variable, with pneumonia and tumor being the most common.

Abnormal Scintiphotogram without Pulmonary Pathology

A second group of patients were found to have abnormal scintiphotograms and normal chest x-rays; a combination of findings was seen in 15 of the patients, eleven of whom had a good clinical story for pulmonary embolism. Further evaluation based on pulmonary angiography, lung biopsy or autopsy confirmed the clinical diagnosis in all of these patients. The final diagnosis was pulmonary embolism in 12 of these patients.

The remainder of the patients had negative scintiphotograms. A few of these were found to have abnormal chest x-rays with the remainder having normal chest x-rays. There were no patients in this group with negative scintiphotograms who were proved later to have pulmonary emboli. Such diseases as pneumonia without consolidation and pulmonary metastases showed abnormal chest x-rays, whereas the vast majority of the patients with normal chest x-rays were



PA CHEST

PULMONARY ARTERIOGRAM

SUPINE CHEST

Fig. 2 — Pulmonary studies on a 37-year-old male with dyspnea and fatigue. Roentgenograms showed few abnormalities and a pulmonary arteriogram was normal. Photoscans show multiple areas of decreased activity on two occasions. Diagnosis of pulmonary embolization was confirmed by lung biopsy.

found to have some cardiac abnormality.

Case Studies

The following are four examples from our studies showing results obtained from both the rectilinear scanner and scintillation camera.

Case No. 1

Figure 1 shows the roentgenogram and scintiphotogram of a 52-year-old white male who was admitted with the acute onset of chest pain which was thought to be related to a coronary thrombosis or to multiple pulmonary emboli. On admission on February 3, 1965, the chest film revealed a small right pleural effusion. On February 17, 1965, the patient complained of severe chest pain on the right side and hemoptysis. The chest x-ray at that time revealed some increased density of a diffuse nature in the right lower lung field, and a lung scan showed a marked decrease in perfusion of the right lower lung field and also the right central lung field. The patient continued on a steady downhill course and expired on February 20, 1965.

Autopsy revealed two infarcts in the right base, one of recent onset and one considered to be of several weeks' duration. A large embolus was found in the pulmonary vessels perfusing this lung field.

Case No. 2

Figure 2 shows the results of roentgenographic and scanning procedures performed on a 37-year-old white male who was admitted to the hospital because of progressive dyspnea and fatigue over the past eight months. The clinical impression at the time of admission was multiple pulmonary emboli. A chest film on September 14, 1965, was thought to show relative radiolucency of the left lung and right lower lung when compared to the remainder of the pulmonary parenchyma. A lung scan on the same day showed decreased perfusion in the right upper lung field and left middle and lower lung fields and was interpreted as being most compatible with multiple pulmonary emboli. A pulmonary angiogram was then performed and reported as normal, as was also a repeat chest roentgenogram taken on September 21, 1965. A repeat lung scan on September 20, 1965, showed a continuance of abnormalcy with marked decrease of perfusion of the right upper lobe and almost all of the left lung, with some improvement in the perfusion of the left base. A lung biopsy showed microscopic findings compatible with previous pulmonary emboli.

Case No. 3

Figure 3 shows the pulmonary studies performed on a 47-year-old white male who was admitted to the hospital with hemoptysis and some dyspnea. Chest film at the time of admission showed a relatively well localized, round density in the left inferior hilus; subsequent work-up revealed carcinoma of the lung. A lung scan showed a marked decrease of perfusion in the left midlung field, an example of how the pulmonary vasculature can be compromised by intrapulmonary masses. The pulmonary angiogram likewise showed marked decrease in perfusion of the midportion of the left lung.

Case No. 4

Figure 4 shows the roentgenograms and scintiphotograms obtained on a 67-year-old white male whose only complaint was the sudden onset of severe dyspnea. He had had similar episodes of dyspnea one year before when he had had thrombophlebitis. Plain chest films were interpreted as normal. The patient received 5 millicuries of 99m technetium tagged with macroaggregates of albumin, followed by scintiphotograms obtained with our scintillation camera. Three areas of decreased activity were seen, two involving the midportions of both lungs and one involving the right apex. A pulmonary arteriogram was obtained which showed delayed perfusion to the same areas previously demonstrated on the scintiphotograms, as well as the deposition of a saddle embolus involving both pulmonary arteries. This embolus was found at surgery to have markedly attenuated the lumen of the arteries to the right apex, right midlung field as well as the left midlung field.

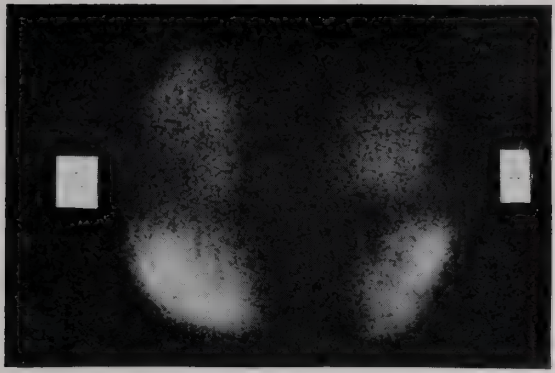
PA CHEST SCINTISCAN PULMONARY ARTERIOGRAM

Fig. 3 — Pulmonary studies on a 47-year-old male with carcinoma of the left lung. Note the localized density in the left inferior hilus on the roentgenogram. Photoscan shows decreased activity in the left midlung field proved to be due to vascular occlusion of the pulmonary vessels to this area by the carcinoma as shown on pulmonary arteriogram.

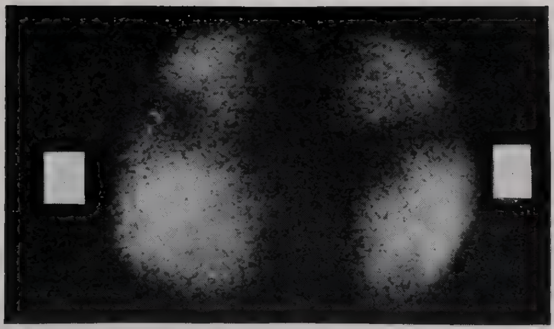
Discussion

Since the macroaggregates are caught in the vascular system of the lung there is an area of absent or decreased activity on the scintiphotograms because the injected material is not able to get to the peripheral pulmonary vascular bed. Therefore, lung scintiphotograms show areas of absent or decreased perfusion related to abnormalities in lobar or segmental distribution of pulmonary blood flow. It is therefore apparent that any process which compromises or occludes the pulmonary vasculature will produce an abnormal lung scintiphotogram, a finding which appears to be most useful in the diagnosis of pulmonary embolization. The particular finding considered most significant in pulmonary embolization is a crescent-shaped area of decreased perfusion in the peripheral lung field.[2] It is well known that pulmonary embolization can occur without infarction of the lung tissue; consequently lung scintiphotography is of particular value when embolization is suspected but no evidence of an abnormality on plain chest roentgenograms is seen.

Other pulmonary abnormalities may also cause decreased or absent activity. Among

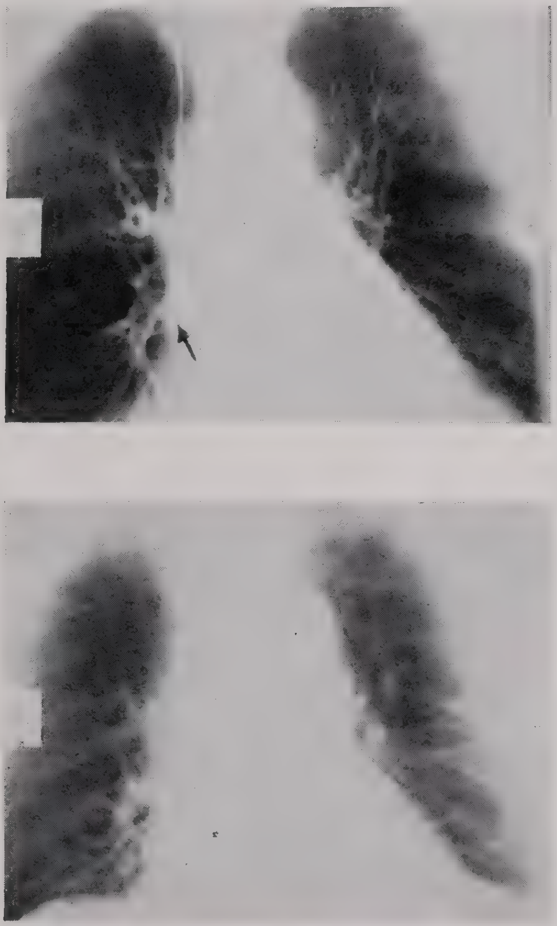


HIGH POSTERIOR LUNG



MID POSTERIOR LUNG

LOW POSTERIOR LUNG
LUNG SCINTIPHOTOGRAMS
TAKEN PA AND DISPLAYED
IN POSTERIOR PROJECTION



ARTERIAL PHASE
VENOUS PHASE
PULMONARY ARTERIOGRAM

Fig. 4 — Scintiphotograms and pulmonary arteriogram on a 67-year-old man whose only symptom was sudden dyspnea. Note the three areas of absent activity on the scintiphotograms as well as a portion of the large saddle embolus (arrow) on the arteriogram.

these are tumors, pneumonia in a state of consolidation, atelectasis, pulmonary sequestration, pulmonary abscesses, and large pleural scars.[5] In these latter cases the chest x-rays are invariably indicative of pulmonary pathology.

Conclusions

It is our impression that scintiphotography of the lung is a valuable diagnostic tool, especially in the diagnosis of pulmonary embolization in which there has not been evidence of infarction on plain chest films. Although we cannot make a definite diagnosis of pneumonia or tumor by the use of scintiphotography of the lung we still feel that serial scans in these diseases can very readily follow the course of the disease. It is also our opinion that the use of short half-life isotopes in relatively high dosages with the use of the scintillation camera is perhaps preferrable to conventional rectilinear scanning because it takes less time to perform, therefore causing the patient less discomfort. We are able to obtain this information much more rapidly by administering relatively larger amounts of radioisotope than if we were to use low doses of longer half-life isotopes using the scintillation camera. One disadvantage of the camera, however, is its limited field necessitating several views in the examination of a larger individual.

Acknowledgments

The authors acknowledge with thanks the technical assistance of Mrs. Lucille Gomez, Miss Norma Constantino and Mr. Stephen Bostrom.

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Of the Remedies for Mania

Such as should be applied to the mind through the medium of the body . . .

1. The first remedy under this head should be blood-letting . . . It should be copious on the first attack . . . From 20 to 40 ounces of blood may be taken at once, unless fainting be induced . . . It will do most service if the patient be bled in a standing position. The effects of this early and copious bleeding are wonderful in calming mad people . . . 3. Solitude is indispensably necessary . . . 4. Darkness should accompany solitude . . . 5. A standing position of the body . . . 6. Low diet, consisting wholly of vegetables, and those of the least nutritious nature . . . 7. Purging. Calomel and jalap should be preferred (in complicated cases) . . . 10. Blisters to the ankles and wrists in alternation, in order to attract the disease from the lodgment in the brain and, after the complete reduction of the pulse . . . to the neck and head . . . 11. Cold in the form of air, water, and ice . . . To favour its partial action, the hair should be cut off and shaved from every part of the head. — Benjamin Rush (1745–1813)

By the time you learn the lessons of life you're too old and weak to walk to the head of the class. — George Goings

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Democracy would not need so many to defend it, if it had more on whom it could depend. — Sun Dial.

The Use and Abuse of Thyroid Hormone

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PHYSICIANS CAN BE classed as conservative or liberal in advising thyroid hormone for their patients. The purpose of this paper is to present a conservative approach to the use of thyroid hormone. The areas of abuse and the specific indications for thyroid hormone will be discussed.

General Considerations

There are several gradations between euthyroidism** and hypothyroidism. It is important to detect abnormalities in thyroid function by a careful history, physical examination and appropriate laboratory tests, but not by any one of these alone.

A hypothalamic humoral factor, so-called thyrotropin-releasing factor, stimulates the synthesis and discharge of anterior pituitary thyrotropin. Thyroid-stimulating hormone stimulates the thyroid gland to secrete thyroid hormone. Thyroxine and triiodothyronine inhibit thyroid-stimulating hormone and probably thyrotropin-releasing factor by a feedback mechanism.[1] In euthyroid patients the administration of desiccated thyroid inhibits endogenous production of thyroxin by suppressing thyroid-stimulating hormone. Thus, exogenous thyroid up to a certain point merely acts as replacement for endogenous thyroxin, causing no definite change in the clinical status or thyroid function tests. Greer[2] found that within one week of thyroid administration the thyroid gland activity, as measured by the I-131 uptake, could be greatly reduced. In over 90 per cent of patients the daily dose required was 60 to 180 mg. As much as 600 mg. per day was required in some subjects to accomplish this effect.

In thyroid-treated euthyroid patients, approximately two weeks are required for the thyroid uptake of I^{131} to become normal after cessation of therapy. Some patients require several months for complete recovery.

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**See Test Your Word Score Page 1267.

Until the thyroid gland takes over active production of hormone again, the patient may not feel well; he may experience fatigue, malaise, muscular aching and emotional lability (Fahrquason phenomenon). A few patients following cessation of thyroid therapy have a "super-rebound" of sufficient magnitude to cause permanent thyrotoxicosis. Patients treated with thyroid continuously for many years experience just as much return of thyroid activity as those treated for a few weeks. Thus, there is no reason to give thyroid hormone to euthyroid patients.

Thyroid Function Tests

The serum cholesterol determination, due to its wide variations in normal, is the least useful test of thyroid activity. The basal metabolic rate is an unreliable test in mild hypofunction of the thyroid. The I^{131} uptake is better in the diagnosis of hyperthyroidism but is of much less value in establishing the diagnosis of hypothyroidism. The thyrobinding protein index and the erythrocytic triiodothyronine uptake are more subject to laboratory error and interference by drugs.

The serum protein-bound iodine (or butanol-extractable iodine) is the most reliable test for hypothyroidism. The usual range of normal is 4 to 8 micrograms per cent.

The Achilles reflex, observed visually or by means of an electromagnetic recording device, is a simple and helpful adjunct in the diagnosis of thyroid disorders.[3]

Hypometabolism Without Myxedema ("Metabolic Insufficiency")

The syndrome of hypometabolism without hypothyroidism occurs more commonly in women than men and between the ages of 15 and 40 years. The subjective complaints are fatigue, weakness, cold intolerance and constipation. Physical examination reveals obesity and brittleness of hair and nails without the classical skin and deep tendon reflex changes of hypothyroidism. The basal metabolic rate is usually between minus 15 and minus 30. Some of these patients receive initial benefit from thyroid hormone, and with increased doses more subjective benefits result. Other patients derive no benefit from treatment.

Levin[4] studied such a group of patients with the basal metabolic rate in the minus range and a normal protein bound iodine and I^{131} uptake. Over 75 per cent of patients complained of constipation, fatigue and tension, and 40 per cent had cold intolerance. Treatment with thyroxin, triiodothyronine and a placebo in a controlled double-blind study demonstrated that the thyroid hormones had no beneficial effect.

More intensive studies are necessary to establish the exact nature of this disorder. The defect may well be in general body metabolism. Some physicians advise a trial of thyroid hormone in this group. Unfortunately, patients may be lost to follow-up and just keep renewing their prescriptions for thyroid hormone. The author does not give thyroid to these patients.

Thyroid Hormone in Obstetric and Gynecologic Diseases

Thyroid hypofunction in both the pregnant and nonpregnant phases requires careful clinical appraisal of the patient, combined with thyroid function tests, and occasionally a therapeutic trial.

During pregnancy the basal metabolic rate shows a progressive rise beginning in the fourth month and rises to about plus 16 at term. The determination of the protein bound iodine in pregnant women also shows a trend towards higher values, reaching levels of 11.2 micrograms per cent. The rise takes place over no particular period of the pregnancy; it occurs in the sixth or up to the twelfth week. The elevation in protein bound iodine does not correlate with the rise in basal metabolic rate. Pregnant women also have slower reflexes than nonpregnant.

Pregnancy is rare in the hypothyroid female, and the incidence of spontaneous abortion is increased should pregnancy occur; but pregnancy itself does not alter hypothyroidism. Russell[5] felt that correcting low protein bound iodine levels improved the prognosis for the successful continuation of pregnancy, thus minimizing threatened and habitual abortion. Singh and Morton[6] showed that low protein bound iodine levels were not associated with abortion and that increased levels did not guarantee against abortion; they also questioned the wisdom of giving thyroid hormone routinely in threatened or habitual abortions. Naumoff and Shook[7] felt that pregnancy caused thyroid decompensation with less available thyroid hormone in women with "low thyroid reserve" leading to spontaneous abortion.

Correcting hypothyroidism is also important in the nonpregnant period to prevent infertility, anovulation, and menorrhagia.[8]

The emperic use of thyroid hormone without clinical or laboratory indications other than infertility, menorrhagia, or first trimester abortion has lead to its discredit.

Thyroid Hormone in Other Diseases

Deafness and occasionally tinnitus and vertigo can be present in myxedema. Some otologists use thyroid hormone empirically, with nicotinic acid, procaine, or lipoflavenoids in treating hearing problems of uncertain cause.[9] Neurologists observe that patients with narcolepsy or those who are "sleepy normal" are referred to them for evaluation, and they are commonly on thyroid hormone.[10]

Without clinical and laboratory evidence of hypothyroidism, these are misuses of thyroid hormone.

Specific Indications for Thyroid Hormone

Thyroid hormone is indicated in the following disorders:

1. Primary or spontaneous myxedema of adults (Gull's disease) or of children (juvenile myxedema).
2. Cretinism.
3. Post-surgical or radioiodine hypothyroidism (cachexia strumipriva).
4. Pituitary myxedema (part of panhypopituitarism, isolated thyrotropin deficiency, pituitary dwarfism, or acromegaly.)
5. Hypothyroid phase of acute granulomatous thyroiditis.
6. Hashimoto's thyroiditis (with or without hypothyroidism).
7. Simple goiter.
8. Hyperophthalmia of Grave's disease (pituitarigenic oculopathy).
9. Cancer of the thyroid gland.

General Considerations in the Use of Thyroid Hormone

The adequacy of the dose of thyroid hormone in treating myxedema is best evaluated by the clinical response. There is a considerable difference in the requirements of patients for thyroid hormone as indicated by the observation that some can take 180 mg. daily without signs of overdosage, whereas others can take 600 mg. with impunity. The usual therapeutic dosage in otherwise healthy patients is 60 to 180 mg. (1 to 3 grains) daily. A single daily dose is adequate particularly with desiccated thyroid and 1-thyroxin. There are several thyroid preparations available and the physician is advised to become familiar with and use only one or two of them:

Types of Thyroid	Dose Equivalents
Desiccated thyroid	60 mg. (gr. 1)
Sodium 1-thyroxin (Synthroid (R))	0.1 mg.
2-L-triiodothyronine (Cytomel (R))	25 mcg.

If doubt exists regarding the original diagnosis of hypothyroidism, the patient should be advised to stop thyroid hormone for two months and return for a clinical re-evaluation and appropriate thyroid function tests. Some endocrinologists advise a thyroid-stimulating hormone test to assess the potential thyroid function of the patient while he is being treated with thyroid hormone. Thyroid-stimulating hormone will stimulate the uptake of I^{131} by the thyroid gland, which is suppressed by exogenous thyroid hormone but is potentially capable of function.

The requirement for thyroid hormone falls with advancing years and the dose may therefore have to be decreased. Thyroid hormone should be used with caution in patients with angina pectoris, recent myocardial infarction, congestive heart failure, adrenal insufficiency, anoxic states, diabetes mellitus and psychiatric disorders.

Some of the more common specific indications for thyroid hormone will be discussed briefly.

Primary Myxedema of Adults

The disease is insidious in onset with cold intolerance, coarse and dry skin and hair, decreased sweating, pallor, slow and husky voice, edema of eyelids and hands, weight gain, deafness, menorrhagia, hypertension, bradycardia, low pulse pressure, slowing of the deep tendon reflex return (Woltman's sign), slow cerebration with poor memory, irritability, and possible psychosis and decreased drug tolerance.

If the clinical features are equivocal and the laboratory studies borderline, it is best to observe the patient at monthly intervals rather than "muddy the water" by beginning treatment. One should remember that since the treatment is lifelong, diagnostic certainty is important.

Funduscopic and visual field examination by confrontation should be done on all patients with apparent primary myxedema. Head x-rays to rule out a pituitary tumor should be obtained.

Before starting thyroid hormone in any patient with primary myxedema, one must inquire carefully about angina and related cardiac disorders and exercise caution in administration if these is present.

Pituitary Myxedema

This condition can be caused by an isolated thyrotropin deficiency, accompanying panhypopituitarism, pituitary dwarfism, or acromegaly. Myxedema may dominate the clinical picture, but one should always inquire and examine for features of hypoadrenocorticism and hypogonadism. A thyroid-stimulating hormone reserve test for the detection of mild secondary hypothyroidism has been described by Studer et al.[11] and is analogous to the use of metopyrone in evaluating pituitary ACTH reserve. In cases of panhypopituitarism, thyroid hormone should be administered along with or after the beginning of adrenocortical replacement therapy. If thyroid extract is given inadvertently before cortisone, there is the danger of precipitating an adrenal crisis.

Hashimoto's Thyroiditis

This is an auto-immune disease primarily of women between the ages of 15 and 40 years. The goiter is usually symmetrical, irregular and rubbery. If the disease is of recent onset, the patient will be euthyroid, but if longstanding, hypothyroidism commonly exists. Laboratory tests usually reveal an elevated sedimentation rate, abnormal zinc or thymol turbidity tests, a protein bound iodine and BEI difference of greater than one, and elevated alpha-2 and gamma globulins on serum protein electrophoresis. If surgery is not indicated, the administration of thyroid hormone suppresses thyroid-stimulating hormone, thereby shrinking the goiter and relieving hypothyroidism if it exists.[12]

Hyperophthalmopathy of Grave's Disease

The severe exophthalmos of Grave's disease is without a doubt the most difficult manifestation to treat successfully. As it can be brought on or aggravated by thyroid surgery, many physicians use thyroid hormone, particularly if the hyperthyroidism is mild. It is thought that thyroid hormone suppresses thyrotropin and exophthalmos-producing substance. Other adjunctive methods of treatment are with Lugol's solution, steroids, diuretics, small doses of roentgen therapy to the retro-orbital tissues and, of late, surgical decompression of the retrobulbar space.[13]

Simple Goiters

Simple goiter is commonly due to hypoiodinism. It is also called endemic goiter, is apt to appear in mountainous regions and is common in the Great Lakes area. These patients are usually euthyroid but occasionally hypothyroidism is found. Simple goiter predisposes to the development of adenomatous goiter, thyrotoxicosis and cancer, and many endocrinologists feel that this and all goiters, unassociated with thyrotoxicosis, should be treated with thyroid hormone indefinitely.

Thyroid Cancer

Thyroid hormone plays an integral part in the treatment of thyroid cancer. Most thyroid cancers and their metastases, except for advanced cases with anaplastic carcinoma, are dependent on thyrotropin for their growth. Thyroid hormone is administered before and/or after surgery to suppress thyrotropin, also serving as replacement therapy if a total thyroidectomy has been done.

In some cases of early papillary carcinoma, thyroid alone is the drug of choice, as advised by many endocrinologists. In follicular carcinoma, if radio-iodine therapy is anticipated following surgery to destroy any remaining tumor, thyrotropin and thyroid hormone are both given. Generally speaking, patients with thyroid cancer need thyroid hormone just short of producing thyrotoxicosis for the remainder of their lives.[14]

If a thyroid nodule does not take up radioactive iodine ("cold nodule") and will not shrink on suppressive thyroid therapy, it should be removed surgically. Thyroid nodules should be watched carefully, since the question whether thyroid carcinoma will shrink under suppressive therapy or metastasize during observation has not been answered.[15]

Summary

This paper has presented a conservative approach to thyroid hormone therapy. Hypothyroidism from several possible causes, the hyperophthalmia of Grave's disease and thyroid cancer are the most common specific indications for its use.

A vast number of conditions are being treated with thyroid hormone despite the absence of definite evidence of hypothyroidism. Thyroid hormone has little benefit in such nonspecific and isolated conditions as obesity, chronic fatigue, deafness, dry skin, menorrhagia or infertility.

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On Being a Patient

There was no doubt that having pneumonia had been a stupendous experience; it was almost like being outside the world altogether, or at any rate like being in a world of dream-work so terrific that I afterwards thought of it as a sort of supernatural revelation. Those vague multitudes under enormous flame-lit arches — what could they have been if they were not something to do with death? Even now I can recover my awed sensation of having been away from life, of having had a glimpse of something for which I had no words. — Siegfried Sassoon (1886–)

Discretion keeps us from questioning, delicacy keeps us even from guessing.
— Comtesse Diane

On Longevity

In his Makrobiotik Christoph Hufeland (1762–1836) gives an account of several instances of exceptional longevity. One of these relates to Terentia, the wife of Cicero, who, despite the sore trials to which she was subjected, and despite the occasional attacks of gout with which she was afflicted, attained the great age of 103 . . . Two other Roman women are mentioned by Hufeland as having attained a great age. They were both of them distinguished actresses. The first one, whose name was Luceia, began her theatrical career at a very early age and was 112 years old on the occasion of her last appearance on the stage; her entire theatrical career having covered a period of one hundred years. Galeria Copiala is the name of the other actress, who was at the same time famous as a danseuse. Ninety years after her first appearance on the stage she took part in a complimentary performance in honor of Pompey; and even at a still later date she acted in a play which was intended to celebrate the distinguished reign of the Emperor Augustus.

Hufeland mentions further instances of great longevity which he had gleaned from Jewish history, and from these I select the following: Abraham lived to be 175 years old, and his wife, Sarah, the only woman of that remote period of time of whom we possess a precise knowledge, died at the age of 127; Isaac attained the age of 180; Jacob lived to be 147; Ishmael, a son of Hagar and a man of warlike habits, attained the age of 137; and Joseph, the next to the youngest of Jacob's sons, a political leader and a man of great wisdom, died at the age of 110. Moses, a man of conspicuous intellectual capacity and possessing a strong will, lived to be 120 years old . . . Joshua, who led a very active life and was a good deal of a warrior, died at the age of 110; and Elisha, who despised all the conventionalities of life and cared nothing for wealth, lived far beyond the limit of 100 years.

The Greek philosopher Pythagoras, who recommended care in the choice of one's food, moderation in eating, and the cultivation of gymnastic exercises, attained a good old age. He claimed that after a man reached his eightieth year, no matter how great an age he might afterward attain, he should be reckoned among those who have ceased to live.*

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*Buck, Albert, B.A., M.D.: The Dawn of Modern Medicine. New Haven: Yale University Press, 1920, p. 30-31.

Whatever is agreeable to You, O Universe, is so to me, too. Your operations are never mis-timed. Whatever Your seasons bring is fruit for me, O Nature. From You all things proceed, subsist in You, and return to You. — Marcus Aurelius

Apocrypha

Honour a physician with the honour due unto him for the uses which ye may have of him: for the Lord hath created him. For of the most High cometh healing, and he shall receive honour of the King. The skill of the physician shall lift up his head: and in the sight of great men he shall be in admiration. — Ecclesiasticus

Retroperitoneal Fibrosis:

A Confusing Syndrome*

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RETROPERITONEAL FIBROSIS is an unusual disease of obscure etiology characterized by a retroperitoneal fibrotic plaque causing constriction and loss of function of the involved structures. It may be a self-limited disease and regress; or it may progress and require surgical intervention. Males are more likely to develop the disease than females in a ratio of 3:1. It occurs between the fourth and sixth decades of life. It was a great rarity twenty years ago; but it now is a well-recognized entity.

Etiology

No specific cause of the disease has been found. Factors believed to be implicated have been: sensitivity to an autogenic agent with antibody response; infection spread by lymphatics, vasculitis, and prolonged use of methysergide (Sansert), ergotamine tartrate (Cafergot), and other drugs. The disease was not described adequately before 1948. Subsequently, many new drugs have been introduced which may have contributed to the increased incidence of the disease.

Symptoms

The early phases of the disease when the tissue reaction is first taking place may be without symptoms or cause vague abdominal complaints. As fibrosis and contraction occur during the late or healing stage, the structures within the area are affected and cause symptoms. Constriction of the great vessels may cause intermittent claudication. Edema of the lower extremities and hydrocele occur when the vena cava and spermatic veins are obstructed. Cases have been reported in which biliary and duodenal obstruction occurred. In one case, retroperitoneal fibrosis simulated carcinoma of the pancreas. Vague abdominal and loin pain is a common manifestation. Anemia and weakness are usually present. Oliguria and anuria occur when the disease reaches its most serious phase. Ormond's[2] original classical description is of a middle-aged man with anorexia and backache in whom oliguria and axotemia developed.

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*Presented at the Monthly Surgical Meeting, The Swedish Hospital, Minneapolis, Minnesota, July 23, 1965.

Diagnosis

Excretion urograms may be diagnostic. Hydronephrosis and hydro-ureter result from constriction of the mid-ureters; however, no difficulty is usually encountered in the retrograde passage of the ureteral catheter. The mid-ureters are displaced toward the midline by fibrous constriction. Lymphangiograms have demonstrated the disease before changes in the urinary system have occurred.

Treatment

When the diagnosis is made, ureteral obstruction can be relieved by ureterolysis. Both ureters can be approached through a long mid-line incision. The right ureter is reached through the posterior peritoneum by mobilizing the ascending colon and duodenum medially. On the left side, the ureter is reached by mobilizing the sigmoid colon. Both ureters can be freed rather easily because there is a good line of cleavage and the ureters are not invaded by the fibrous reaction. They are mobilized laterally and need not be intubated. If the diagnosis is obscure and the kidney approached through the flank, temporary nephrostomy can be employed. The value of steroids has not been clearly demonstrated, as some cases of spontaneous remission have been recorded. In cases of drug allergy, discontinuance of the medication has resulted in regression without the need of surgery.

Pathology

Grossly, the fibrosis is most dense where the ureters cross the iliac vessels and may involve an area from the aortic bifurcation to the renal arteries. The extent and amount of inflammation may vary considerably. Microscopically, there are dense bundles of collagenous tissue with typical connective tissue cells associated with inflammation. In some cases, there has been a resemblance to periarteritis nodosa.

Case Report

A 52-year-old white male crane operator was first seen at The Swedish Hospital in October 1963, at which time his main complaint was right lower quadrant pain of variable duration and intensity for eight to ten years. There was no history of ingestion of drugs. Gallbladder, colon, excretory urograms, upper gastrointestinal, chest, lumbosacral and spine films failed to explain the cause for his discomfort. Routine laboratory studies were normal. It was noted that the sedimentation rate was elevated on two occasions, being recorded as 53 mm. and 57 mm. per hour. The patient was discharged with a diagnosis of functional spastic bowel.

He was readmitted to the hospital in November 1963, with the same complaints. Again it was noted that the sedimentation rate was elevated to 65 mm. per hour. Exploratory laparotomy was entirely negative except that the mesentery to the ilium was thickened, irregular, nodular and somewhat cobblestone on its surface, and there was erythymatous injection in some areas. The mesentery was biopsied and a retrocecal appendix was removed. The biopsy revealed fat with inflammatory margins, and the section of the appendix suggested subsiding appendicitis.

The patient continued to have right lower quadrant pain and always felt below par. On May 25, 1964, he developed right testicular swelling with hydrocele and was readmitted to the hospital three days later with a history of not having passed any urine for 48 hours and having bilateral lumbar pain. On catheterization there was no urine in the

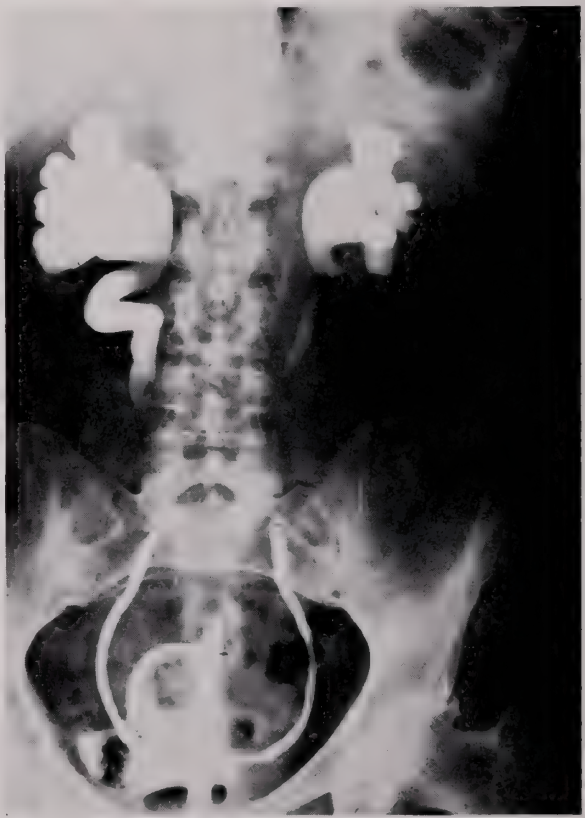

Fig. 1 — Retrograde uretero-pyelogram showing compression and medial displacement of mid-ureter with hydro-ureter and hydronephrosis above.

bladder. The patient was pale and edematous and had an uremic odor to his breath. The blood pressure was 150 systolic and 90 diastolic. Laboratory findings on admission were: wbc. 6,100; normal differential; BUN. 67; Co_2 14.7; chloride 102; sodium 136; potassium 6.2; hemoglobin 9.5; and red blood cells 3,380,000. The following day, the blood urea nitrogen was 97 mgm. per cent. A small amount of urine was obtained which revealed packed red blood cells, pus cells and a 4-plus albumin. The patient was then cystoscoped, and under local anesthesia #4 catheters were passed up each ureter to the renal pelves without meeting any resistance. They drained immediately with a copious rapid drip of dilute urine. The catheters were left in place as it was obvious that the patient had a bilateral hydronephrosis. Bilateral retrograde pyelograms revealed both mid-ureters were compressed and both ureters deviated toward the midline with a moderate degree of hydro-ureter of the proximinal ureters and hydronephrosis bilaterally.

The next day the blood urea nitrogen fell to 49 mgm. per cent; two days later it was down to 27 mgm. per cent. The patient was then re-explored under general anesthesia through a long mid-line incision. There was a mass of fixed, hard, white, woody fibrous tissue extending upward from the sacral promontory to the first lumbar vertebra and laterally to the tips of the transverse processes which included the great vessels and mid-ureters. These structures were completely encased in fibrous material and could not be identified. Both ureters were included in the mass for 2½ inches. Below the mass the ureters were of normal caliber; above the mass they were dilated and freely movable. Both ureters were freed easily and mobilized laterally away from the fibrous mass. The remaining defect was obliterated by approximating retroperitoneal fat and peritoneum.

Histologic study of the biopsy specimen showed fibrofatty tissue with extensive chronic inflammatory change. The tissue was heavily infiltrated by numerous lymphocytes, a few neutrophilic and eosinophils, plasma cells, and mononuclear cells, There was no evidence of caseation or malignancy.

Progress

The patient lost 26 pounds while he was in the hospital, much of it fluid. The postoperative course presented no problems and the patient was discharged on the seventh postoperative day. One year later he said that he still had vague lower right quadrant discomfort at times. On excretory urography both kidneys functioned well on the five-minute film. The mid-ureters were displaced laterally as a result of the surgical ureterolysis.

Summary and Conclusion

The etiology of retroperitoneal fibrosis is unknown, but accumulating evidence would indicate that it is probably an immune reaction of collagen tissues. Although drugs and chemicals may be implicated, the cause in most cases remains obscure. The syndrome is confusing and may mimic several abdominal disease conditions until the final stage of bilateral ureteral obstruction occurs. The x-ray and cystoscopic findings are then rather typical. The disease can be alleviated by ureterolysis.

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Except for the Common Cold

I should feel myself ungrateful if I did not testify to my enormous respect and gratitude to the medical profession, and really, on the whole, the doctors I have known have been, I think, among the finest men of my acquaintance. I may have been very fortunate, but that has been my experience. And I am thinking not only of their skill — though I think I should think even more of them if they had discovered how to prevent and how to cure a common cold — but also I have found them always the kindest and wisest friends. And I cannot speak too highly of their wonderful generosity in money matters, a generosity far surpassing what I have found in any other profession. — Dean Inge: Address to Students of the London Hospital, 1933.

The Theriac Cure-All*

The most called-for remedy in all the countries at the time of Harvey . . . was the famous theriacum** or theriac, a remedy as old as Galen, probably older, and which has undoubtedly made more "cures" than any other drug compilation. Even in Galen's time, the prescription for it was extremely complex and a little bit later it came to be spoken of as a "calendar" prescription because it had as many or more ingredients in it than the days of the month . . . It was a veritable gunshot prescription with the shot so scattering that it was sure to hit something, provided it was sent anywhere near the general direction of the object at which it was aimed.

Claude Bernard, the great French physiologist, has told the comical story of it. As a boy he worked in a drug store. He found there was one remedy that was sold more than any other in this small town in western France. This was the theriac. It was kept in a great big jug and the bottles of those who brought in their own were filled with it, or other bottles were supplied to customers for a consideration.

It was a cure for colds as well as for indigestion, for the various bronchitises as well as for heart trouble, for depression and nervousness, for both mind and body. The druggist boy who sold so much of it felt that the whole mystery of medicine was contained in this one remedy. Soon in the round of his duties as a nascent pharmacist he found the secret of it. All the spoiled medicines in the store went into the theriac jug. Whenever a mistake was made in compounding a prescription it was poured into the jug. Whenever there was a drug preparation left standing so long that there might be a reasonable suspicion that the strength of it had either diminished or increased until they did not care to dispense it in the regular fashion, that, too, went into the jug. When by some chance a label came off a bottle and it was not quite sure what was in it the rule of the store was: "Dump it into the theriac jug." Fortunately all the really active ingredients were so diluted that the resulting compound was not likely to do harm, and it is easy to understand that this hodge-podge of drugs of all kinds had a thoroughgoing mediciny taste and was sufficiently nauseous to make even the most hardened veteran taker of drugs feel that he was getting something for his money.

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*Walsh, James J., M.D., Ph.D., Sc.D.: Cures, D. Appleton and Co., New York, 1923.

**See Test Your Word Score Page 1267.

The Unwritten Law

Of course everybody knows that Doctors never say anything unkind about each other, it is part of their Unwritten Law and a sore trial to nearly all of them. The only person to whom a Doctor can say exactly what he thinks about another Doctor is his Wife. That is why practically all Doctors are married. — Joyce Dennys: The Over-Dose.

Of a sane man there is only one safe definition: he is a man who can have tragedy in his heart and comedy in his head.— Chesterton

Partial Anomalous Pulmonary Venous Return

A Hypoplastic Right Lung to the Inferior Vena Cava (Scimitar Syndrome*)

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Anomalous venous connection between the right lung and the inferior vena cava is a rare congenital defect which is often associated with abnormalities of the bronchovascular structure of the right lung. Oxygenated blood from the lung enters the right heart through the inferior vena cava resulting in a left-to-right shunt with its deleterious effects. Pulmonary venous return may be routed to the left atrium by a closed extracardiac operation, but cardiopulmonary bypass is often required. Anomalies of the right lung may be dealt with as indicated at the same operation. Recent experience with the successful surgical treatment of a patient with anomalous connection between the venous drainage of the right lung and the inferior vena cava prompted us to make this report.

Case Report

A six-year-old Puerto Rican girl was admitted to the Texas Children's Hospital on November 16, 1964, with a two-year history of easy fatigability and recurrent bouts of palpitation with rapid heart action.

When the patient was seven months old, the parents were informed that she had a heart murmur; when she was three years old a diagnosis of patent ductus arteriosus was made by a cardiologist. The child developed slowly for her age and sustained numerous pulmonary infections, some of which required hospitalization for treatment.

In 1962, at four years of age, the child underwent division and suture of a patent ductus arteriosus. At that time a "vascular ring" was interrupted by dividing a retro-esophageal right subclavian artery. The following year in Puerto Rico cardiac catheterization demonstrated an anomalous venous return of the right lung into the infradiaphragmatic portion of the inferior vena cava. In addition a stenosis was noted at the junction of the inferior vena cava and the right atrium, causing collateral flow through the azygos system. Multiple stenoses of the peripheral pulmonary arteries were also demonstrated.

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See Test Your Word Score Page 1267.

See editorial page 1255 by J. J. Garamella, M.D.

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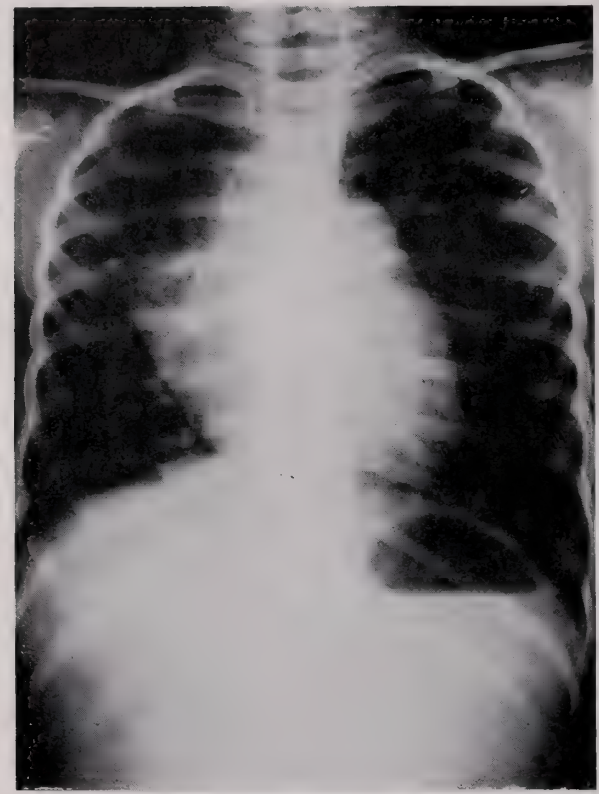

Fig. 1 — Anteroposterior roentgenogram of chest showing scimitar-shaped shadow along right border of heart.

Physical Findings

On physical examination the blood pressure was 100/68 in the left arm and the pulse rate was 90 (regular). No pulses were present in the right arm. Her height and weight (36 pounds) placed her in the twenty-fifth percentile on the anthropometric chart. Examination of the heart revealed gross enlargement. There was a Grade IV continuous murmur over the left axilla and adjacent left posterior chest, with a greatly accentuated split-second heart sound. The lungs were clear to percussion and auscultation. There was no clubbing of the digits and no peripheral edema.

Laboratory Studies

An electrocardiogram demonstrated right ventricular hypertrophy and first degree A-V block. Laboratory data included a white blood cell count of 8,100, a normal urinalysis, a hemoglobin of 13.3 gm. per cent, a hematocrit of 41 per cent, and a blood urea nitrogen of 8 mg. per cent. Roentgenograms of the chest disclosed moderate cardiac enlargement with increased pulmonary vascularity. A crescent-shaped shadow was present along the right border of the heart (Figure 1).

Cardiac Catheterization Studies

Cardiac catheterization revealed an oxygen saturation of 95 per cent in the inferior vena cava near the diaphragm. Pressure in the main pulmonary artery was 72/35 mm. Hg., while the systemic pressure was 136/78 mm. Hg. The catheter was passed up the inferior vena cava into an anomalous venous trunk draining the right lung. A pressure gradient of 28 mm. Hg. was recorded between this trunk and

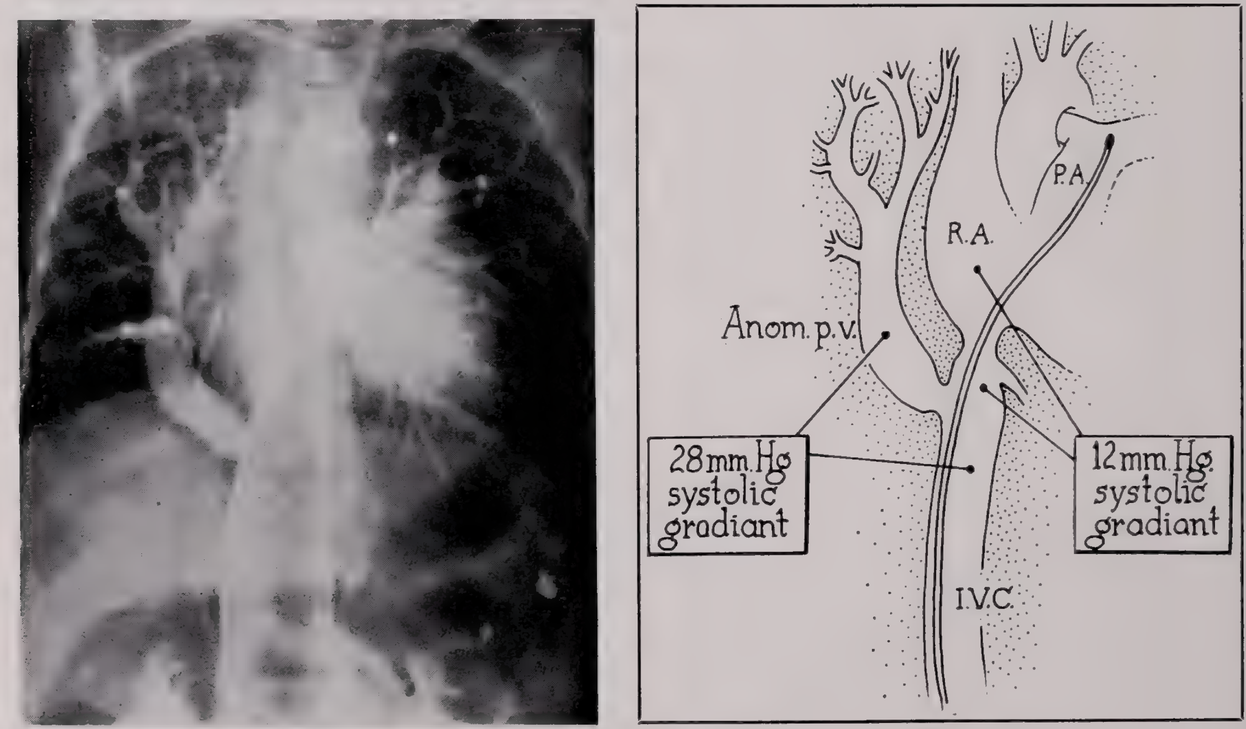

Fig. 2-a

Fig. 2-b

Fig. 2 — a. (left) Angiocardiogram with catheter in pulmonary artery. Note large vein draining entire right lung and traversing diaphragm to enter inferior vena cava. b. (right) Drawing of a. showing anatomy of veins and gradients present.

the inferior vena cava below the hepatic veins. A second pressure gradient of 12 mm. Hg. existed between the inferior vena cava near the diaphragm and the right atrium. Angiocardiography was performed by injecting contrast medium into the pulmonary artery. The pulmonary veins from the right lung converged in a large trunk that descended along the right border of the heart and narrowed just before it entered the inferior cava below the diaphragm (Figure 2). Enlarged azygous and hemiazygous veins were seen to serve as collateral pathways to carry pulmonary and systemic venous blood around the partially obstructed inferior vena cava into the superior vena cava. The oxygen saturation of blood at the junction of the superior vena cava and azygous vein was 90 per cent.

The Operation

An operation was performed on November 23, 1964. The patient was placed in the supine position with the right side elevated 45 degrees. A transverse incision was made in the right fourth interspace transecting the sternum but not entering the left pleural space. Exploration revealed that the pulmonary veins of the right lung converged into a single trunk approximately 12 mm. in diameter that descended between the heart and lung to pierce the diaphragm. Compensatory dilatation of the azygos vein, inferior vena cava, and the right atrium was present. The right lower lobe was enclosed in a separate pleural envelope and was supplied by a systemic artery entering its lower surface through the diaphragm. The middle lobe was normal.

After mobilization it was apparent that the anomalous pulmonary vein was not sufficiently long to permit an anastomosis between it and the left atrium without undue tension or kinking. Consequently, the vein was divided near the diaphragm and anastomosed end-to-side to the right atrium near the septum. An intracardiac diversion was then performed with cardiopulmonary bypass using a disposable plastic bubble oxygenator primed with 5% dextrose in water. A longitudinal incision in the right atrium allowed visualization of the anastomosis on the posterior wall of the right atrium near an intact septum. A small portion of septum, 1.5 cm. in diameter, was excised posteriorly near the anastomosis. An oval patch of pericardium sutured to the superior, anterior, and inferior margins of this aperture and then to the posterior wall of the right atrium to the right of the anastomosis permitted blood to be channeled from the right pulmonary vein into the left atrium. The right atrium was closed and cardiopulmonary bypass discontinued (Figure 3). After resumption of satisfactory cardiac action, the sequestered right lower lobe was removed. The patient had an uneventful postoperative course and was discharged ten days following operation. She was re-evaluated nine months after operation and was asymptomatic. Cardiac catheterization at that time revealed moderate pulmonary hypertension (62/30 mm. Hg.) and no shunt.

Examination of the pulmonary tissue showed an aberrant position of the vessels along the hilar aspect of the right lower lobe. Many of the pulmonary arteries were of diminished caliber and there was intimal fibrosis and disruption of elastic fibers in the media. Large and small pulmonary veins exhibited moderate increase in thickness of their walls, and intimal sclerosis was present.

Discussion

In a classic review of 100 cases of anomalous pulmonary venous return published in 1942, Brody[4] found only three patients with abnormal drainage from the right lung into the inferior vena cava. Since the advent of angiocardiography, several excellent articles have appeared on this subject.[1,10,11,12,14,17,23,29] Interest in anomalous pulmonary venous drainage has mounted with the development of methods for accurate clinical and laboratory diagnosis, since corrective surgery is now possible.

X-ray Findings

The "scimitar syndrome" is a descriptive term applied by Neill[23] to a condition that originally included a hypoplastic right lung with a systemic arterial supply and venous

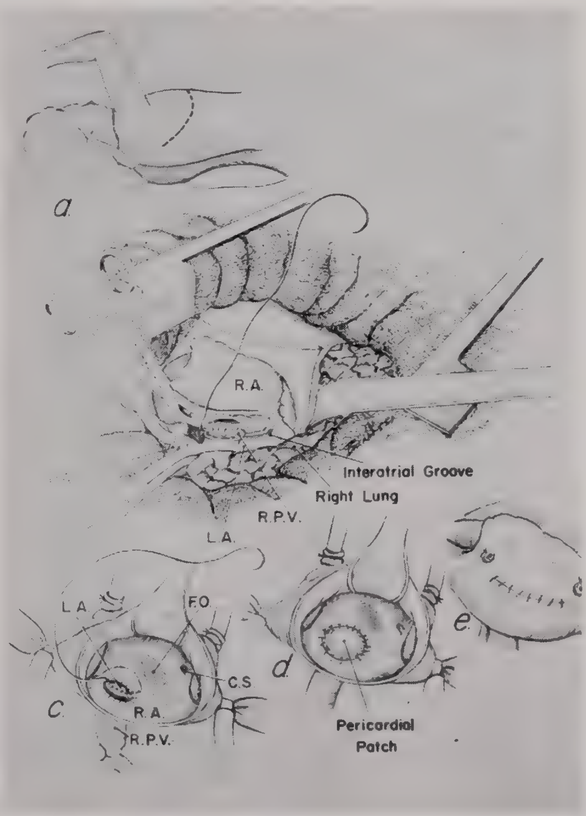

Fig. 3 — Artist's illustration of operative procedure with creation of interatrial septal defect, shunting blood returning from the right pulmonary vein to the right atrium and through the septum into the left atrium.

TABLE
Surgical Treatment of Patients with Scimitar Syndrome

Authors	Age Yrs.	Sex	Add. Venous Drainage	Assoc. Heart Defects	Assoc. Rt. Lung Defects	Procedure	Results and Comments
Drake & Lynch (1950)	14	M	Sup. pulm. v. to lt. atrium	None	No middle lobe	Rt. lower lobectomy w/division of inf. pulmonary vein	Improved, though cough and mild exertional dyspnea persisted
Cooke (1951)	20	M	Sup. pulm. v. to L.A.	None	—	Exp. thoracotomy only	Unchanged
Halasz et al. (1956)	8	M	Azygous lobe to L.A.	Probable VSD	Hypoplastic middle lobe	1st op. thoracotomy only. 2nd op. right pneumonectomy	Cardiac murmur persists, dyspneic
	7	F	—	—	Hypoplastic right lung	Rt. pneumonectomy	Recovered
	6 mo.	F	—	—	Bronchial anomalies, art. supply to RU & RML from aorta	Right pneumonectomy	Expired - Massive mediastinal emphysema, subphrenic abscess
Kirklin et al. (1956)	32	F	—	Mod. ASD	None	Transplanted rt. pulm. v. to post wall atrium with atrioseptopexy	Recovered and improved (1st total correction)
Gilman et al. (1957)	—	—	Upper lobe joined to L.A.	—	— —	Transplanted pulm. v. to rt. atrium, ASD created and atrioseptopexy	No description
Risch and Hahn (1958)	—	—	—	ASD	—	Rt. pulm. v. to left atrium, ASD sutured	Only brief description of case
Koch & Silva (1960)	41	F	—	—	Only 2 lobes	Transplantation of pulm.v. to left atrium	Recovered
McCormick (1960)	13	F	—	—	—	Transplantation of P.V. to L.A.	Cited by Shumacker
Neill & Assoc. (1960)	2-½	F	—	—	Hypoplasia rt. lung, systemic arteries to rt. lung	Rt. pneumonectomy	Expired (?)
Blondeau & Assoc. (1961)	12	M	Sup. V. to left atrium	—	—	Right lower lobectomy	Expired with infarction of right lung and part of left

TABLE (Continued)

Mpalas & Cooley (1962)	44	F	Hypoplastic vein to left atrium	—	—	Rt. pneumonectomy	Improved
	5-½	M	—	—	—	Transplantation of pulm. v. to left atrium	Improved
O'Brien & Assoc. (1962)*	36	F	Small v. to L.A.	—	Hypoplastic rt. lower lobe	Transplantation of pulm. v. to left atrium (? open heart)	Expired—Pleural effusion—Complete atelectasis of rt. lung
Frye & Assoc. (1962)	22	F	—	ASD	None	"Complete repair"	Improved
Zubiate & Kay (1962)	22	M	Sup. vein to L.A.	None	—	ASD created & teflon patch placed over pulm. v. to newly created defect to shunt blood into left atrium	On total cardiopulmonary 105 min. patch atelectasis and atrial flutter p.o. Eventually improved
Kittle & Assoc. (1962)	28	F	Small V from mid-portion of lung to L.A.	None	—	Transplanted PV to LA on cardiopulmonary bypass	P.O. fever, pain and right pneumonitis; readmitted. Apparently cleared subsequently
De Bakey (1963)	19	F	—	None	Sequestrated RLL	Transplantation of pulm. v. to L.A., closed technic	Recovered
Johansson & Silander (1964)	Not described		—	—	—	Transplantation of pulm. v. into left atrium	P.O. bleeding, fibrillation and basal atelectasis of rt. lung—eventually recovered
Ellis & Assoc. (1964)	20	M	—	—	—	"Total correction"	Recovered and improved
Schumacker (1964)	14	M	Sup. v. to SVC and one v. to IVC	ASD	—	Graft diversion of pulm. v. into left atrium thru ASD under cardiopulmonary bypass	No details given of result. Details of 2nd case in series not described
Yonehiro, Hallman & Cooley (1965)	6	F	—	Prev. ductus ligation	Hypoplasia rt. lower lobe, vasc. abnormalities	Transplantation of rt. pulm. v. to rt. atrium with atrioseptopexy to direct blood to left atrium under cardiopulmonary bypass	Recovered and improved

*In addendum author notes three additional patients "Successfully treated" . . . No details given.

drainage into the inferior vena cava. A scimitar-shaped vascular shadow presented a characteristic appearance paralleling the right cardiac silhouette and represented the anomalous pulmonary vein descending to join the inferior vena cava. The diagnosis can usually be entertained on viewing the plain posteroanterior roentgenogram of the chest (Figure 1). The right upper lung field may appear relatively avascular, and the right hemithorax is frequently smaller than the left. Because of these anatomical changes the right atrium is prominent and the heart appears to be shifted towards the right.

Anatomical Anomaly

Often the right lung is a mirror image of the left lung, having no, or only a rudimentary, middle lobe. Hypoplasia of the right lower lobe may be present. Occasionally the right superior pulmonary vein empties normally into the left atrium while one or more of the remaining pulmonary veins form a common trunk that may enter the portal vein or the infra or supradiaphragmatic portion of the inferior vena cava. In this type of partial anomalous pulmonary venous return, arterialized pulmonary venous blood from the right lung recirculates through the right heart instead of passing into the systemic circulation by the normal route through the left heart. Hemodynamically this represents a left-to-right shunt, increases the work load of the heart, and leaves the patient with essentially a functionless right lung. In the present case a stenosis at the junction of the inferior vena cava and the right atrium resulted in augmentation of the collateral flow through the azygous vein. With relative obstruction of the inferior vena cava, the azygous and hemiazygous veins become the principal means by which venous circulation is sustained, connecting as they do with the superior and inferior venae cava. The unique participation of the azygous system in this patient is reflected in the catheterization data which demonstrates blood with increased oxygen content (90 per cent) at the junction of the superior vena cava and azygous vein.

Intracardiac Malformations

The most common intracardiac malformation associated with partial anomalous pulmonary venous connection is an atrial septal defect. Shumacker[27] reports an associated atrial septal defect or stretched foramen ovale in 90 per cent of patients with partial pulmonary venous return to the right atrium or superior vena cava, but in only 11 per cent of such patients with drainage to the inferior vena cava. In patients with findings consistent with an atrial septal defect, Frye and his colleagues[12] emphasized the presence of a split-second heart sound as an important diagnostic clue to the presence of partial anomalous pulmonary venous return. Wide splitting of the second heart sound is frequently described in patients with the scimitar syndrome[17,18,22] and was present in our case.

Pulmonary Abnormalities

Abnormalities such as agenesis or hypoplasia of part of the right lung are also associated with anomalous pulmonary venous drainage from the right lung to the inferior vena cava. Systemic arteries arising from the aorta and supplying the right lung are also found in these individuals. Indeed, Kittle and his associates[17] have described this condition as a "vena cava bronchovascular syndrome" consisting of a triad of anomalies involving the right lung. This triad has (1) anomalous pulmonary venous connection, (2) abnormal bronchi, and (3) systemic pulmonary arteries. Because of the frequency of associated pulmonary abnormalities, bronchoscopy and bronchography may be valuable in the preoperative evaluation of these patients.

Clinical Manifestations

Previous authors[2,11,12,14,21,23,28] have described the benign course in many patients with scimitar syndrome. Certainly many are totally asymptomatic when first seen. O'Brien's[24] three patients all had multiple normal pregnancies, indicating that this condition may produce few cardiac symptoms and may be compatible with survival to adult life. Patients, however, may complain of easy fatigability and dyspnea and may develop recurrent respiratory infections. Although some authors have advised conservative treatment for these patients, an aggressive surgical approach has more recently been advocated.[5,8,16,25,27,28,31] The demonstration of a large pulmonary blood flow and elevation of the pulmonary artery pressure in association with a large left-to-right shunt constitutes a definite indication for surgical intervention. As emphasized by some authors[5,10,12] the prognosis in patients with this condition is probably the same as for a patient with an atrial septal defect as far as hemodynamic changes are concerned. Therefore, operative correction to prevent heart failure and subsequent pulmonary vascular changes should be advocated. The obvious disadvantage of a "functionless" right lung constitutes an additional indication for operative correction. Shumacker[27] advises early surgery in individuals with the vena-cava-bronchovascular syndrome because of the likelihood of pulmonary infection and because of the left-to-right shunt with its attendant hemodynamic disturbance.

Therapy

Resection of pulmonary tissue with normal bronchial supply is neither advisable nor desirable and should be reserved for those cases in which a complete repair is impossible.

Neill,[23] in discussing a patient with scimitar syndrome and severe pulmonary hypertension who had expired following pneumonectomy, felt that the pulmonary artery pressure increased in the remaining lung to a point incompatible with life. Ferencz,[11] in reviewing this article, indicated that the scimitar-shaped pulmonary veins had no etiologic significance in the development of pulmonary hypertension, although the two conditions may coexist. Recently Wiederanders and his associates[32] studied the effects of pulmonary resection on pulmonary artery pressure and found that following thoracotomy and resection of less than one lung, the pulmonary artery pressure was little influenced. Pulmonary artery pressure, however, was frequently markedly elevated after pneumonectomy. They concluded that more than one fourth of the vascular bed must be removed to alter the pressure relationship. Thus, if sufficient pulmonary vascular bed is removed, pulmonary hypertension may develop.

In 1956, Kirklin and his colleagues[16] indicated that it was hazardous to occlude one pulmonary artery in a patient with severe pulmonary hypertension. In the presence of severe pulmonary hypertension they concluded that transplantation of an anomalous pulmonary venous connection was probably unwise, since such a procedure would require temporary pulmonary artery occlusion to prevent pulmonary edema during the period of pulmonary venous occlusion. With the availability of extracorporeal circulation, this consideration should not be a deterrent to operation in patients with scimitar syndrome and pulmonary hypertension.

Since 1950 the surgical treatment of the scimitar syndrome has been reported in only 23 patients (Table). Early surgical attempts were limited to pulmonary resection, especially pneumonectomy. In 1956, Kirklin[16] reported the first complete correction of this condition by transplantation of the anomalous right pulmonary vein to the posterior right atrial wall and diversion of blood into the left atrium by means of a closed atrioseptopexy. Since then only twelve additional cases of total correction have appeared in the literature (Table). Only one death occurred in this latter group; this was a 36-year-old patient who died of postoperative pulmonary complications.

The most effective technique of repair appears to be anastomosis of the anomalous right pulmonary vein to the left atrium wherever possible. If the length of the vessel precludes this, the vein should be anastomosed to the posterior aspect of the right atrium, and blood diverted from this ostium into the left atrium by the insertion of a patch sutured about an opening in the atrial septum (either naturally occurring or surgically created), using cardiopulmonary bypass. Abnormalities of the right lung may be dealt with as indicated.

Conclusion

Anomalous drainage of venous blood from

the right lung into the inferior vena cava occurs by means of a large trunk that forms a crescent-shaped shadow along the right border of the heart. When combined with anomalies of the right lung, the name scimitar syndrome has been applied to this complex. Surgical treatment of this anomaly is reviewed and operation recommended when symptoms become significant.

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18-22 May be secured from the author or the reprints

Gulliver's Travels — Jonathan Swift*

Gulliver — On Avariciousness

"In some fields of his country, there are certain shining stones of several colors, whereof the Yahoos (men) are violently fond; and when part of these stones are fixed in the earth as it sometimes happeneth, they will dig with their claws for whole days to get them out, and carry them away, and hide them by heaps" in their jewel boxes; that he had once by way of experiment privately removed a heap of these stones from the palace where one of his Yahoos had buried it: whereupon the Yahoo, missing his treasure —— began to pine away, would neither eat nor sleep, nor work, till he (the master) ordered a servant privately to convey the stones into the same hole, and hide them as before; which, when his Yahoo had found, he presently recovered his spirits ——; but took care to remove them to a better hiding place; and has ever since been a very serviceable brute."

— Heritage Press, 1940

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*See Minnesota Med 49:1080, 1966.

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Medial Approach

HARRISON H. FARLEY, M.D.
ROBERT L. TELANDER, M.D.
CLAUDE R. HITCHCOCK, M.D., Ph.D.*
Minneapolis, Minnesota

REVASCULARIZATION PROCEDURES in the lower limb for arteriosclerotic occlusion of the superficial femoral artery must be individualized because of variations in the extent of disease found to be present on surgical exploration. Whether the occlusion is corrected by endarterectomy or bypassed with a plastic prosthesis or autogenous vein depends to a degree on the personal preference of the operating surgeon.[1-3] Endarterectomy has proved to be successful, but if it is to be performed over any considerable length of vessel, bits of roughened intima may be left behind with a propensity towards reocclusion. The ready availability of the plastic prosthetics has given great impetus to the growth of peripheral vascular surgery, but long-term follow-up studies[4,5] have revealed a rather high rate of late occlusion. The problems of excessive foreign-body reaction and infection are real and mitigate against the use of prosthetics below the inguinal ligament.

Abstract

There are occasions when a bypass procedure, which has been done to revascularize an arteriosclerotic extremity, fails and reoperation becomes necessary. In the hands of Farley et al. an alternative procedure, wherein the saphenous vein is removed and reimplanted, providing an anastomosis between the profunda femoris and the popliteal arteries avoids the previous surgical procedure by making a medial approach. They have found two advantages to this approach and have encountered no disadvantages.

Editors' Note: This manuscript was published in Minnesota Medicine 49:400, 1966. The title was inadvertently incomplete. Because of the significance of this manuscript the title page is hereby reprinted and an abstract attached.

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*Professor of Surgery, University of Minnesota and Chief of Surgery, Hennepin County General Hospital.

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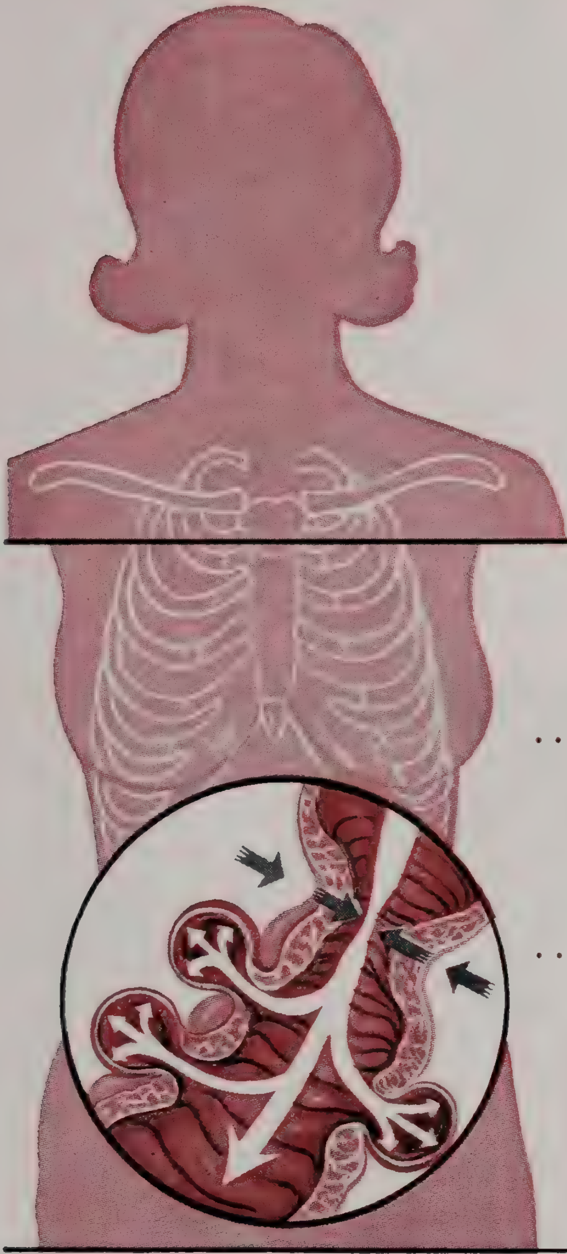

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Editorials

Scimitar Syndrome

"THE SCIMITAR SYNDROME" is a malformation of the heart, lungs, and blood vessels producing a left to right shunt of varying magnitudes. The main feature of the malformation is partial or complete drainage of the right pulmonary veins into the inferior vena cava. Associated malformations may be found as abnormal systemic arterial supply to the right lower lobe; dextrorotation and dextroposition of the heart, hypoplasia of the right lung and pathologic changes in the bronchial tree and parenchyma of the right lung.

A simple anteroposterior film of the chest may be diagnostic, showing the crescent-shaped vascular density adjacent to the right cardiac border which closely resembles a Turkish sword (scimitar).

Park in 1912 described the pathology of the disease and Dotter in 1949 made the first clinical diagnosis of this anomaly. With increasing refinements in diagnosis and potential for surgical cure, reports on this subject have appeared with increasing frequency.

In this issue Yonehiro, Hallman, and Cooley* detailed the highlights of the pathology, hemodynamics and clinical features of lesion and reported a case successfully operated by them after vagaries in diagnosis were overcome.

The surgical alternatives for correction are: closed anastomosis of the aberrant vessel to the left atrium, pulmonary resection removing the shunt, and lastly, anastomosis of the anomalous pulmonary vein to the right atrium with repartitioning of the atria with a pericardial patch as carried out by the authors with cardiopulmonary bypass.

Correction of the shunt without the sacrifice of pulmonary function by pulmonary resection is an ideal goal. Pulmonary resection, however, may be indicated in certain circumstances and has produced satisfying results. With increasing technical skills and refinements in the use of extracorporeal circulation, the excellent results reported will serve to expand the indications for surgical correction.

Joseph J. Garamella, M.D.
Minneapolis, Minnesota

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*See page 1243.

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Auto-Immune Disease

CURRENT THEORIES on the interrelationships between immunity, auto-immunity, and leukemogenesis owe a great deal to imaginative and inquiring clinical observers. The speculations published in the May issue by Good and his colleagues* developed from a large series of observations originally stimulated by a patient with "acquired agammaglobulinemia" who was studied in 1953. This patient had low levels of immunoglobulins and was severely deficient in immunological reactivity but, paradoxically, had an "auto-immune disease," namely rheumatoid arthritis. He was found to have a mediastinal mass which proved to be a benign thymoma. Intrigued by this extraordinary case, Good and a series of collaborators embarked on a lengthy and continuing series of experiments which have helped to elucidate the role of the thymus in the physiology of immunity. Their data indicate that the thymus is essential to the development of full immunologic competence in the mouse, and also to leukemogenesis in this animal. In the chicken the bursa of Fabricius has similarly been shown to be essential for immunologic maturity and also for leukemogenesis. Both of these organs appear to be "source" tissues capable of directing the development of the "peripheral" lymphoid tissue. Good suggests that there may be two lymphoid systems in higher mammals, one directed by the thymus and another directed by an organ analagous to the chicken bursa, which may be located in the appendix, as in the rabbit, or at some other site. They postulate that the thymic system is primarily concerned with immunologic recognition, while the "bursa" system controls production of the various immunoglobulins.

Numerous observations have been recorded from both experimental studies and human disease which suggest involvement of the thymus in the development of auto-immunity. For example, thymic abnormalities have been recorded in lupus erythematosus and myasthenia gravis. Several laboratory examples are also cited by Good. Perhaps the most intriguing is the development of red cells coated with globulin (Coombs-positive) in rabbits which are thymectomized and appendectomized at birth. Some of these rabbits have also developed amyloid disease and other lesions usually attributed to immunologic processes, despite the fact that the animals have become immunological cripples as a result of the surgical procedures. The exact mechanisms which produce this series of events have yet to be worked out. Obviously, the problems involved are important and challenging ones which will probably have a major bearing on both auto-immune disease and leukemia in man.

The Minneapolis group has approached the problems of auto-immunity and leukemia from the background of work on the thymus. It is of interest that other workers have also suggested relationships between leukemia and auto-immunization before the unifying role of the thymus was appreciated. Dameshek and Schwartz in 1959,[1] with the background of years of clinical observation of patients particularly with lymphoproliferative disorders, auto-immune hemolytic anemia and ITP, indicated many points of similarity between leukemia and auto-immunization. They suggested that in both types of disease some change occurs in the growth habits of certain white cell tissues, leading to a proliferation of abnormal cells, and speculated that repeated aberrant immunologic responses might eventually give rise to neoplastic proliferations. The occurrence of immunologic abnormalities in patients with lymphoproliferative disorders is well known. It has been observed that in many patients with chronic lymphocytic leukemia or lymphosarcoma, ionizing radiation or alkylating agents can act as "trigger mechanisms," initiating the development of auto-immune complications such as hemolytic anemia, thrombocytopenic purpura, or vasculitis.[2] These patients are frequently deficient in many of the normal immunologic responses. Thus, there may well be analogies between such patients and Good's adult rabbits which, after thymectomy, appendectomy and irradiation, devel-

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*See Minnesota Med 49:725, 1966.

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oped Coombs-positive hemolytic anemia and other manifestations of auto-immune disease. Multiple myeloma, macroglobulinemia, and Hodgkin's disease, are other disorders which appear to manifest a spectrum of combined leukemic and immunologic proliferation and immunologic deficiency.

There are many pitfalls in the interpretation of data on auto-immune disease. Several forms of immunologic purpura have been shown to be due not to auto-antibodies to platelets, but to antibody to drugs or to foreign platelet antigens. Similarly, although a positive Coombs test is frequently taken as evidence of auto-immunity, several cases of Coombs positive hemolytic anemia have been reported which were due to antibodies directed not to the red cells, but rather to penicillin administered to the patient. Good's suggestion that auto-immune disease may be due to virus or mycoplasma infection occurring in the setting of immunologic deficiency is an intriguing one, but these infections remain to be demonstrated.

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Hip Subluxation in Early Infancy

It is certainly true that treatment of congenital hip in the infant is highly dependent on early recognition. Results are far superior when treatment is instituted within the first several months of life. Congenital dysplasia of the hip, in general, is managed easily; and excellent results can be expected, provided early use of the pillow splint is instituted. Congenital dislocation of the hip, on the other hand, carries a more guarded outlook, although it must still be recognized and treated as early as possible, since best results depend on this.

Ortolani's sign is unreliable within the first two weeks of the newborn period, when the infant is still under the influence of maternal hormones and many falsely positive clicks can be elicited. Limited abduction of the flexed hip is the most reliable sign in the newborn child to indicate the need for radiographic examination.

Preliminary traction is important before closed reduction is attempted. The traction should be continued for several weeks to allow the capsular structures to stretch out gradually so as to reduce the possibility of the development of avascular necrosis in the capital femoral epiphysis. This well-known complication is related to the forcefulness of attempts at reduction and to the failure to use preliminary traction. The report of only one case of avascular necrosis in 19 dislocations attests to the relatively gentle reductions accomplished by Gustilo and co-workers.[1] The proper position for holding patients after closed reduction is the position of maximal stability, as determined clinically and radiographically. This may be the frog-leg position, but often the Lange position (internal rotation and abduction of the leg) is better initially, especially when marked anteversion of the femoral neck is observed.

If closed reduction is not possible, open reduction is carried out, when, generally, the position of best stability is found to be that of internal rotation. Excessive anteversion of the femoral neck is best managed by derotational osteotomies which probably should be performed more often than they currently are.

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Rochester, Minnesota

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Detection and Localization of Intracranial Lesions

THE RELIABLE detection, by means of remote or external sensing devices, of physical or chemical substances concentrated in an intracranial pathologic process has intrigued investigators for many years. It is now apparent that certain radioactive isotopes can be chemically combined with compounds which, under certain circumstances, will become concentrated in detectable amounts within some of these lesions. One of the most useful of these isotopes is 197-Hg when tagged to Neohydrin. Its value is indicated by the report of Wigdahl, Gilson, Staab, and Loken.* Such developments have been accompanied by improvements in technique so that the procedure has considerable reliability in the detection of neoplastic and non-neoplastic diseases.

In considering these new and exciting procedures, it is tempting to speculate concerning the comparative value of the various techniques designed to reveal intracranial lesions. In the years between the advent of intracranial pneumography and cerebral angiography, opinions concerning the relative merits of pneumoencephalography and ventriculography were subjects of great interest in published reports, professional meetings, and informal discussions. Equally competent investigators preferred one over the other, although there were always certain instances in which one procedure was obviously more suitable. After its general acceptance, cerebral angiography frequently appeared to be in competition with air-contrast examinations, although in many instances the problems could be solved by several of the different techniques. The indications for the most suitable method of initial investigation, however, depend on many factors, including the reliability of the examination and the elements affecting the safety and well-being of the patient. Thus, these procedures are not mutually exclusive.

The development of a reliable brain-scan technique adds another important diagnostic method. It is tempting to hope that, because of its simplicity and usually innocuous effects, it might frequently take the place of more complicated procedures. Unfortunately, like the others, it is not 100% reliable and its execution is rather time-consuming Although considerable statistical information reveals that a positive result of a successfully planned and accurately performed brain scan may indicate the presence of an intracranial pathologic process, a study yielding a negative result, like any other type of examination giving a negative result, does not prove the absence of a lesion. Thus, in the presence of appropriate clinical signs and symptoms, it may be necessary to employ several, if not all, of the available methods before tentatively excluding a pathologic process.

If a lesion can be detected and localized with assurance, such specialized examinations have fulfilled their most important functions. However, the exact nature of several important types of intracranial diseases can be ascertained with considerable accuracy by the judicious application of the appropriate test. This is particularly true of the revelation of aneurysms, A-V malformations, and subdural hematomas by cerebral angiography and of the detection of the size, shape, and position of certain intracranial tumors by means of cerebral pneumography. Therefore, although the brain scan and certain ultrasonic techniques are exceedingly useful methods for the detection and localization of some intracranial lesions, they should not be considered in competition with one another or as mutually exclusive in their application. The physicians in charge are required to select in each instance the test or tests which might be expected to be of most value in the total management of the patient's problem.

Colin B. Holman, M.D.
Rochester, Minnesota

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*Wigdahl, L. O., Gilson, J. M., Staab, E. V., and Loken, M. K.: Brain Scanning with Neohydrin 197-Hg. Minnesota Med 49:411, 1966.

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Discovering Small Bowel Tumors

An article appearing in the April issue* of this journal presents the ten-year collected experience of two Minneapolis hospitals with 32 small bowel tumors. The small number of lesions is in keeping with the low rate of occurrence reported in the world literature.

The low incidence may be an important contributing factor to many of the problems of diagnosis and treatment, primarily because the experience of any individual physician is limited. The early symptoms are usually of a relatively nonspecific nature and are frequently attributed to more common and less dangerous gastrointestinal lesions. Nonspecific therapy is most often prescribed and more extensive diagnostic procedures postponed. While delay is of no great importance in dealing with benign lesions, there is no doubt it may influence the salvage rate where malignant lesions are encountered. All too frequently when symptoms become severe enough to warrant abdominal exploration, the surgeon finds that lymph nodes are involved and peritoneal spread has occurred.

The low survival rate in adenocarcinoma of the small bowel is in keeping with the results of therapy for adenocarcinoma of other nearby organs, namely the pancreas and stomach. The failure of therapy in these instances is directly related to the inability of the physician to make a diagnosis at a time when there is any hope of cure. This deficiency is obviously most marked in carcinoma of the pancreas where the diagnostic dilemma has remained essentially unchanged since the introduction of a definitive radical operation. Despite vigorous application of available diagnostic techniques curable tumors of the pancreas are only rarely detected. This is obviously not as true for small bowel carcinomas.

Minor symptoms such as anemia, pain, weight loss seldom bring a patient to early exploration. In fact, many patients with symptoms and negative physical and laboratory findings, may be classed as psychoneurotics and therapy held in abeyance for a period of months or years. An absolute finding such as an abdominal mass or unrelenting obstruction or profound anemia will usually bring the patient to exploration. In these circircumstances, however, the situation may already be irretrievable.

The surest way to swing most physicians and surgeons from procrastination to action is demonstration of the lesion. In order to accomplish this short of exploration, the medical profession has come to rely almost exclusively on radiological examination. However, the efficiency of roentgenologic diagnosis of small bowel lesions decreases from the duodenum to the jejunum and ileum for the most part because of the length and pliability of the small intestine and the unavoidable overlap of its different portions. Furthermore, the technique of examination is seldom mastered, due to infrequent utilization and because intestinal follow-through series as now practiced provide only intermittent film views of the passage of the barium meal.

In order to obtain continuous filling of the small bowel under direct observation so that added information concerning motility, mucosal pattern, and distendability are available, various modifications of the technique have been proposed, most requiring small intestinal intubation (Schatzki, Blodgett, Hodges, Golden & Dundon). This technique permits the use of dilute barium and allows small segments of the intestine to be filled for more detailed examination. Where the intestine has normal motility a Miller-Abbott tube is best passed by the physician or surgeon on the ward before the patient is taken for x-ray examination. The foregoing techniques enable the roentgenologist to obtain greater contrast at the site of examination and afford a better chance of detecting small or intramural lesions.

Furthermore, it has been reported that while primary carcinomas may involve any portion of the small intestine, they show a predilection for the proximal quarter of the jejunum and the distal quarter of the ileum

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*See Minnesota Med 49:572, 1966.

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in patients with known propensity for taking
cessive quantities of drugs and in patients w
known sensitivity to compounds of similar che
cal structure, e.g., meprobamate.

Side Effects: The only side effect reported with
frequency is sleepiness, usually on higher t
recommended doses. An occasional patient n
not tolerate carisoprodol because of an individ
reaction, such as a sensation of weakness. Ot
rarely observed reactions have included dizzin
ataxia, tremor, agitation, irritability, headache,
crease in eosinophil count, flushing of face,
gastrointestinal symptoms.

One instance each of pancytopenia and le
penia, occurring when carisoprodol was adr
istered with other drugs, has been reported, as
an instance of fixed drug eruption with carisopr
and subsequent cross reaction to meprobam
Rare allergic reactions, usually mild, have inclu
one case each of anaphylactoid reaction with
shock and angioneurotic edema with respira
difficulty, both reversed with appropriate ther
In cases of allergic or hypersensitivity reacti
carisoprodol should be discontinued and appr
ate therapy initiated. Suicidal attempts may
duce coma and/or mild shock and respira
depression.

Dosage: Usual adult dose is one 350 mg. ta
three times daily and at bedtime.

Supplied: Two Strengths: 350 mg. white tab
and 250 mg. orange, two-piece capsules.

Before prescribing, consult package circular.

for the relief
of low back
sprains and strai

SOMA
(CARISOPRODO

Wallace Laboratories, Cranbury, N

26

(Maingot, Kiefer, Dockerty). This fortuitous distribution of lesions should decrease the difficulty and time involved in demonstrating lesions of the proximal jejunum. However, passing a long tube to the distal ileum is a much less practical proposition, and perhaps a greater emphasis should be placed on examination of the distal small bowel by reflux of barium through the ileocecal valve. In fact this occurs relatively frequently during the course of barium enema examination. It has been a common belief that the routine examination of the distal bowel by barium reflux is not only difficult but often impossible due to a competent ileocecal valve present in approximately two thirds of patients. A recent report (Miller & Miller) seems to refute this concept in that a complete examination of the small intestine has been achieved by this procedure, including the proximal jejunum and duodenum in 72 of 75 patients where the examination was attempted. The technique offers the advantages of a barium enema examination of the colon, in that the barium column advances under fluoroscopic observation, permitting the accurate localization of various lesions and the interpretation of mucosal and motility patterns.

A new technique has recently been proposed for the detection of bleeding sites in the stomach or small intestine (Margulis, Baum). It consists of selective catheterization of the celiac or superior mesenteric arteries with injection of contrast media which subsequently appear in the bowel lumen at the bleeding site. Some successes have been reported in the diagnosis of small bowel lesions both in the experimental laboratory and clinical situations. At least for the time being this technique will be limited to large hospital centers.

The problem of the diagnosis and treatment of small bowel carcinomas remains, for the most part, unsolved at the present time. Without question, early diagnosis would increase the salvage rate and allow the fullest use of the radical surgical procedures available at the present time.

Peter A. Salmon, M.D.
Minneapolis, Minnesota

Unsuspected Aortoiliac Arterial Occlusive Disease*

PATIENTS WITH the classical findings of the Leriche syndrome present little difficulty in clinical diagnosis, and operation is usually clearly indicated. Those with incomplete occlusion of the aortoiliac arterial segments may have unsuspected impairment of the blood flow to the hips and lower extremities. Symptoms may not always be the typical effort-claudication but may be described as weakness or paresthesias of the hips, thighs, legs, or feet. The presence of palpable pulses throughout the extremity may be misleading because palpable pulses can occur in the presence of impairment of flow. Exercise will frequently produce a reduction or disappearance of the pulses in such cases. The presence of a bruit over the terminal aorta or iliac or femoral artery is highly suggestive of a stenotic lesion in the region.

Translumbar aortography is indicated in all cases in which there is a suspicion of occlusive vascular disease and in which the symptoms warrant investigation.

Surgical treatment for aortoiliac occlusive disease is effective, and the risk can be quite low. Thus, its application seems justified in most patients who are symptomatic. A bypass grafting procedure has many advantages over endarterectomy but has the disadvantage of introducing a foreign substance.

Unsuspected aortoiliac disease is frequently a cause of failure in the surgical treatment of femoropopliteal occlusive disease because of inadequate inflow into a bypass graft or endarterectomized femoropopliteal segment. Disease in these two regions frequently occurs concomitantly, and it is essential that proximal disease not be overlooked when planning an operation on a distal segment. In many cases, correction of the proximal disease will obviate the need for operation in the distal segment.

Robert B. Wallace, M.D.
Rochester, Minnesota

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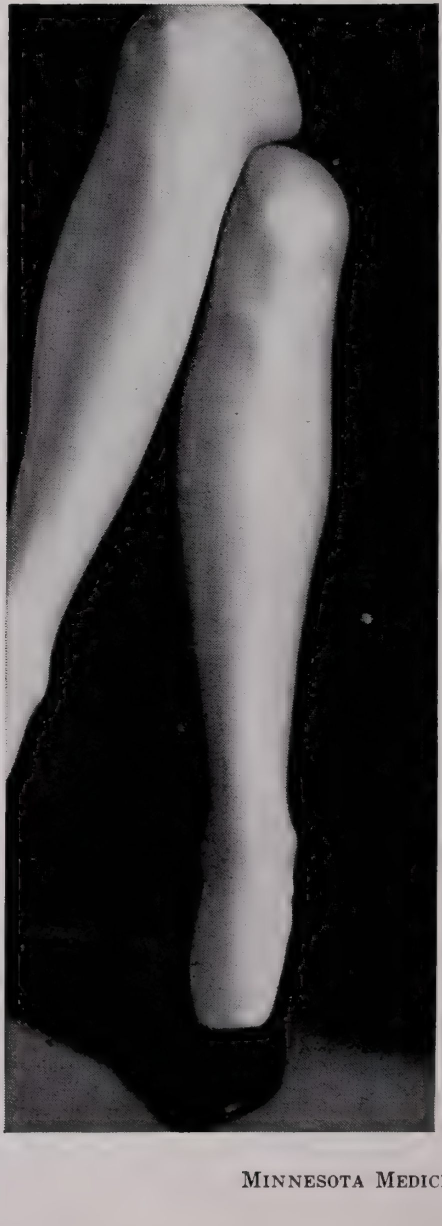
*Mongé, J. J., and La Bree, R. H.: Aortoiliac Occlusion. Minnesota Med 49:566, 1966.

If you can't alarm her
into wearing elastic stockings...

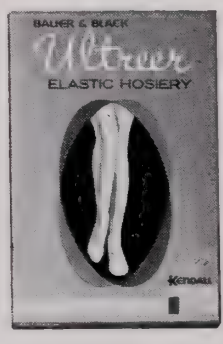
charm her with Ultreer™



You see, a woman simply has no defense against Ultreer Elastic Stockings. They look like lovely support stockings. They feel like lovely support stockings. They're that sheer, and shapely and comfortable.

But that's where the similarities end. New Ultreer fits firmly and evenly over the entire leg. Gives true therapeutic compression necessary to relieve varicose veins and other leg disorders. Each pair provides the therapy you prescribe. And at such a low price, a woman can afford two pairs of Ultreer as easily as she can afford one pair of ordinary elastic hosiery.

Ultreer. What a stocking.



KENDALL
BAUER & BLACK SUPPORTS DIVISION

You May Be Right

The Minnesota State Flower

My photograph was used as the cover illustration and I must point out a rather glaring error in labeling it. The yellow ladyslipper is not the state flower of Minnesota. The state flower is the pink ladyslipper.

G. M. Johnson, M.D.
Bismarck, North Dakota

Editor's Note: Cypripedium Reginae — This is a pink-white ladyslipper and is the Minnesota state flower. The yellow and the purple ladyslippers are also found in Minnesota but are not the state flower.

Test Your Word Score

Maddox rod — *series of parallel glass rods — converts image of candle into a streak of light — presence of heterophoria* (page 1218).

Panacea — *a cure-all remedy* (page 1222).

Cavum septi pellucidi — *fifth ventricle* (page 1224).

Hemimelia — *defects in the limbs* (page 1225).

Scintiphotography — *indicating intensity of radioactivity transmitted to paper grid* (page 1227).

Euthyroidism — *Normal thyroid function* (page 1233).

Theriacum — *antidote against poisonous bites* (page 1242).

Scimitar — *a short curved sword used by the Turks* (page 1243).

Anisocoria — *inequality of pupils* (page 1282).

Elaterium — *dried sediment from juice of squirting cucumber — hydragogue cathartic* (page 1333).

Time is money, and many people pay their debts with it. — Josh Billings

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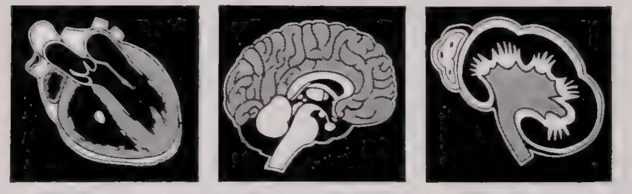
You take my life, when you do take the means whereby I live. — Shakespeare.

SQUIBB NOTES ON THERAPY

Behind continued high blood pressure readings lies the possibility of organic damage[1-13]

MANY OF THE aspects of essential hypertension are unpredictable—either because there are a number of mechanisms involved or because individuals differ in their responses to these mechanisms.[1]

There is one aspect of hypertension, however, that seems, in many cases, predictable. ". . . when the blood pressure is elevated to a marked degree for an adequate period of time, this in itself leads to perpetuation of the syndrome with resulting vascular damage throughout the body."[14] All too often the disease progresses until there is damage to one of three vital organs: the heart, the kidney, the brain.



> "Hypertension is certainly a major factor in the genesis of coronary heart disease, and it is even more important when compounded with obesity."[4]
>
> "[Vascular deterioration] can be clearly seen in the kidney with a degree of damage that can be measured by renal function studies."[10]

". . . most evidence suggests that reduction of blood pressure, when it is too high, not only relieves the heart of excess work but reduces vascular damage."[1]

"In short, treatment is indicated."[1]

Antihypertensive therapy will not restore the blood vessels to normal. Yet many of the vascular changes and symptoms caused by increased blood pressure may be arrested or alleviated when the blood pressure is reduced to normotensive levels.[7]

Reducing the blood pressure helps curtail further vascular damage and improves the prognosis — when damage is not too far advanced before therapy is started.[14] Essential hypertension is an indication not only for treatment, but for *early* and adequate treatment of the patient in question.

Reduce the blood pressure with Rautrax-N

Rautrax-N combines the antihypertensive-tranquilizing action of whole root rauwolfia with the antihypertensive-diuretic action of bendroflumethiazide in one convenient medication. The two drugs complement each other so that smaller doses of both are possible.

Rauwolfia combined with bendroflumethiazide is particularly effective in long-term therapy,[15-17] since beneficial effects do not diminish with continuous daily administration.

For most patients 1 or 2 Rautrax-N tablets daily are sufficient for maintenance therapy. The simplicity, convenience and economy of such a dosage schedule are of particular benefit to older patients.

References: 1. Page, I. H., and Dustan, H. P.: The Usefulness of Drugs in the Treatment of Hypertension, in Ingelfinger, F. J.; Relman, A. S., and Finland, M.: Controversy in Internal Medicine, Philadelphia, W. B. Saunders Co., 1966, p. 95. **2.** Hollander, W.: The Evaluation of Antihypertensive Therapy of Essential Hypertension in Ingelfinger, F. J.; Relman, A. S., and Finland, M.: Controversy in Internal Medicine, Philadelphia, W. B. Saunders Co., 1966, p. 97. **3.** Nickerson, M.: Antihypertensive Agents and the Drug Therapy of Hypertension, in Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 3, New York, The Macmillan Co., 1965, p. 727. **4.** Berkson, D. M.: Indust. Med. & Surg. **32**:371, 1963. **5.** Cohen, B. M.: M. Times **91**:645, 1963. **6.** Lee, R. E., et al.: Am. J. Cardiol. **11**:738, 1963. **7.** Moyer, J. H.: Am. J. Cardiol. **9**:821, 1962. **8.** Moser, M.: New York J. Med. **62**:1177, 1962. **9.** Wood, J. E., and Battey, L. L.: Am. J. Cardiol. **9**:675, 1962. **10.** Moyer, J. H., and Heider, C.: Am. J. Cardiol. **9**:920, 1962. **11.** Moser, M., and Macaulay, A. I.: New York State J. Med. **60**:2679, 1960. **12.** Judson, W. E.: Nebraska M. J. **44**:305, 1959. **13.** Hodge, J. V.; McQueen, E. G., and Smirk, H.: Brit. M. J. **1**:5218, 1961. **14.** Moyer, J. H., and Brest, A. N.: Hypertension Recent Advances, Philadelphia, Lea & Febiger, 1961, p. 633. **15.** Berry, R. L., and Bray, H. P.: J. Am. Geriatrics Soc. **10**:516, 1962. **16.** Reid, W. J.: J. Am. Geriatrics Soc. **13**:365, 1965. **17.** Feldman, L. H.: North Carolina M. J. **23**:248, 1962.

Contraindications: Severe renal impairment or previous hypersensitivity. **Warning:** Ulcerative small bowel lesions have occurred with potassium-containing thiazide preparations or with enteric-coated potassium salts supplementally. Stop medication if abdominal pain, distension, nausea, vomiting or G.I. bleeding occur.

Precautions and Side Effects: The dose of ganglionic blocking agents, veratrum or hydralazine when used concomitantly must be reduced by at least 50% to avoid orthostatic hypotension. Caution is indicated in patients with depression, suicidal tendencies, peptic ulcer; electrolyte disturbances are possible in cirrhotic or digitalized patients. Marked hypotension during surgery is possible; consider discontinuing two weeks prior to elective surgery and observe patients closely during emergency surgery. Rauwolfia preparations may cause reversible extrapyramidal symptoms and emotional depression, diarrhea, weight gain, edema, drowsiness may occur. Bendroflumethiazide may cause increases in serum uric acid, unmask diabetes, increase glycemia and glycosuria in diabetic patients, and may cause hypochloremic alkalosis, hypokalemia; cramps, pruritus, paresthesias, rashes may occur.

Dosage and Supply: Initial dosage, 1 to 4 tablets daily, preferably at mealtime. Maintenance, 1 or 2 tablets daily. Rautrax-N is supplied as capsule-shaped tablets containing 50 mg. Rauwolfia serpentina whole root (Raudixin®), 4 mg. bendroflumethiazide (Naturetin®), 400 mg. potassium chloride.

Also available: Rautrax-N Modified — capsule-shaped tablets containing 50 mg. Rauwolfia serpentina whole root (Raudixin), 2 mg. bendroflumethiazide (Naturetin), 400 mg. potassium chloride. Both potencies available in bottles of 100. For full information, see Product Brief.

RAUTRAX®-N

Squibb Rauwolfia Serpentina Whole Root (50 mg.) with Bendroflumethiazide (4 mg.) and Potassium Chloride (400 mg.)

SQUIBB 'The Priceless Ingredient' of every product is the honor and integrity of its maker.

The Editor's Soliloquy

Euthanasia — To set you straight.*

From time to time one encounters in the popular media a controversial article decrying the humanitarian intentions of the physician in his effort to prolong the life of a patient during a terminal illness.

No doctor keeps a patient alive without good medical or surgical indication. If a patient survives despite apparently imminent death, it is not because the doctor has administered last-moment stimulants; it is because his initial treatment has succeeded against the odds.

Doctors are not waiting at the grave's edge with an intravenous needle to restore pulse and breath to a moribund mummy. Despite the urgent pleas of distraught relatives who almost invariably implore them to "save no expense" they do, in the terminal illness, only what any good Samaritan would do: they show mercy and compassion.

A patient with an incurable disease who is given a reasonably accurate longevity prognosis may not welcome a premature demise, but when the relatives ask, "Can't something be done, Doctor?" or "Can't you show mercy, Doctor?" are they not virtually suggesting that the doctor act as executioner? Would they themselves be willing to administer the hemlock cocktail? Could they bring themselves to wield the lethal syringe?

No patient is miserable in coma nor does he suffer pain when he writhes in unconsciousness. The delirium of fever or uremia is not distressing. In the valley of the shadow there is no anguished groping for a dubious or chimerical hereafter.

Surely no physician performs an emergency procedure just for the sake of producing a "dreadful ordeal from which there can be no survival, but only prolongation of misery." Weighing the pros and cons the doctor carefully calculates the risk. When he decides to take that risk, it is always in the anticipation and with the prospect of relieving pain, providing comfort, restoring health and extending life. Though there may be moments of "artificial prolongation of physical existence" as the physician discharges his ethical responsibilities to the patient, such moments are exceedingly rare.

Would anyone resent resuscitation measures or an oxygen mask for a drowning child, even though well aware that only a few minutes of oxygen deprivation is sufficient to permanently destroy brain function? Would anyone have enough ice in his veins to say, "Let him die"? Modern methods in medicine have conclusively proven the value of external cardiac massage in many instances of cardiac arrest — with complete restoration. Would anyone suggest that the doctor should have declined to perform it — on the chance that mere physical function might remain and brain function cease?

Doubtless most if not all individuals, if they could make the choice, would elect simultaneous extinction of both body and spirit. But who could schedule the optimal moment for that dual passing — and then implement it with dispatch and finesse!

Only when your sands run out is your life finished. Doctors should be charged with neither the responsibility nor the culpability for making it different.

— **Carl O. Rice, M.D.**

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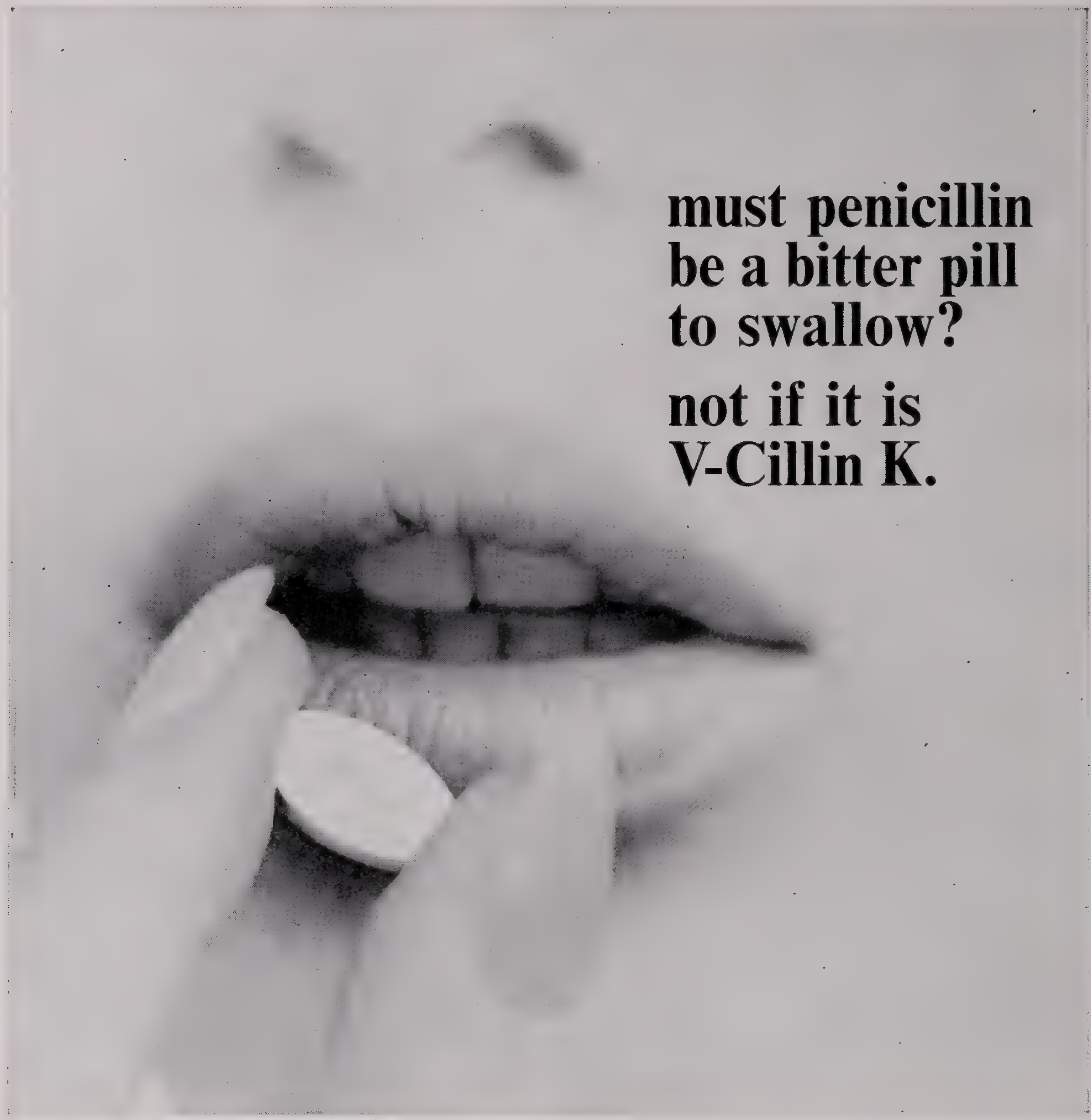
*In response to Elizabeth Davenport Plant in Vogue, June 1966.


must penicillin be a bitter pill to swallow?
not if it is V-Cillin K.

V-Cillin K now has a unique glossy coating that banishes bitter penicillin taste and makes it easier to swallow. Within six seconds (just long enough for the tablet to get past the taste buds), the coating dissolves and the penicillin is ready for immediate absorption into the bloodstream. The patient still gets all the special benefits of V-Cillin K, including consistent dependability . . . even in the presence of food.

Indications: V-Cillin K is an antibiotic useful in the treatment of infections caused by streptococci, pneumococci, and sensitive strains of staphylococci.

Contraindications and Precautions: Although sensitivity reactions are much less common after oral than after parenteral administration, V-Cillin K should not be administered to patients with a history of allergy to penicillin. As with any antibiotic, observation for overgrowth of nonsusceptible organisms during treatment is important.

Usual Dosage Range: 125 mg. (200,000 units) three times a day to 250 mg. every four hours.

Supplied: Tablets V-Cillin K, 125 or 250 mg.; also, V-Cillin K, Pediatric, 125 mg. per 5-cc. teaspoonful, in 40, 80, and 150-cc.-size packages.

V-Cillin K® **Six-Second Barrier to Bitterness**

Potassium Phenoxymethyl Penicillin

600802

Additional information available to physicians upon request. Eli Lilly and Company, Indianapolis, Indiana 46206.

Lilly

PRESIDENT'S LETTER

(Continued from page 1211.)

of a statement entitled "Application of Criteria for Determination of Reasonable Charges." As this statement was accompanied by a request for comments and reaction, and as both documents incorporated major departures from previous statements issued by Social Security Administration, the Advisory Committee requested and received an appointment for July 1st with Social Security Administration officials. Following this appointment and the subsequent issuance by the American Medical Association of a critique of Social Security Regulation #5 and the statement on charges, further meetings to reconcile the points at issue have been arranged and medicine's objections vigorously presented.

Obviously, continuing efforts by the Medical Advisory Committee and the officers of the American Medical Association will be essential in presenting medicine's viewpoint, indicating medicine's opposition to poorly conceived regulations and defending physician rights. Equally obviously, physician awareness of the competence and dedication with which this program is being followed, the complexity of the task and the need for reconciling various reactions to each successive problem will support the Committee by demonstrating united physician backing for the spokesmen for medicine.

RP Buckley M.D.

R. P. Buckley, M.D.
President
Minnesota State Medical Association

Oliver Wendel Holmes, M.D.
To the Young Practitioner

You will remember, of course, always to get the weather-gage of your patient. I mean, to place him so that the light falls on his face and not on yours. It is a kind of ocular duel that is about to take place between you; you are going to look through his features into his pulmonary and hepatic and other internal machinery, and he is going to look into yours quite as sharply to see what you think about his probabilities for time or eternity. . . . No matter how hard he stares at your countenance, he should never be able to read his fate in it. It should be cheerful as long as there is hope, and serene in its gravity when nothing is left but resignation. The face of a physician, like that of a diplomatist, should be impenetrable.

In Flux

Probably the most interesting period of medicine has been that of the last few decades. So rapid has been this advance, as new knowledge developed, that the truth of each year was necessarily modified by new evidence, making the truth an ever-changing factor. — Charles Mayo

Pregnancy

The termination of pregnancy is a mysterious affair. Allergy may be the initial spark that initiates the chain reaction of the contraction of the uterus. The importance of the existence of different individual proteins of mother and child for creating allergic interaction between antigen and antibody must be underlined.

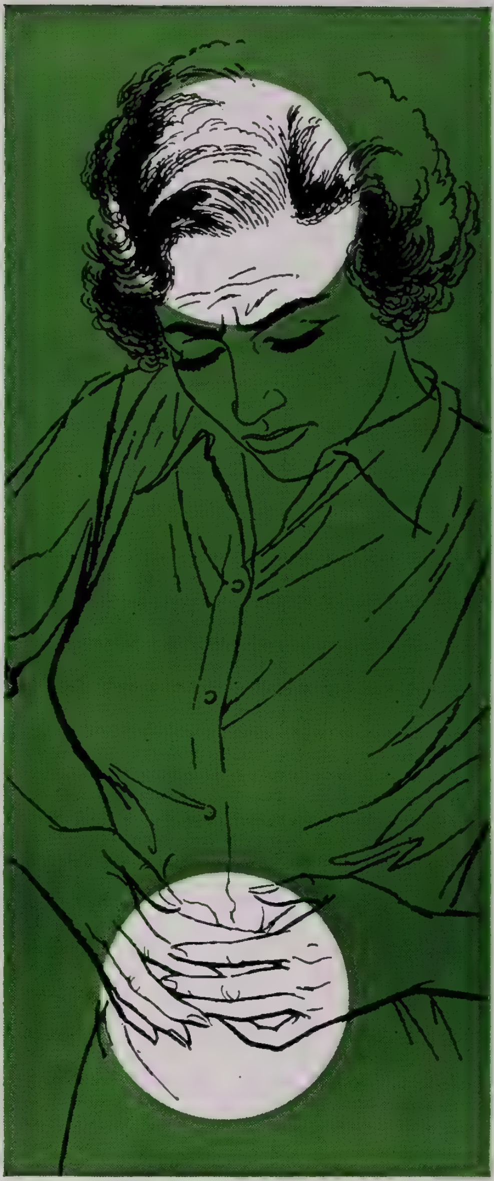
— Bela Shick (1877-)

when agitation accompanies spasm of the 'G. I.' tract.

Butadonna™

BUTABARBITAL SODIUM, 15 MG. (BARBITURIC ACID DERIVATIVE)
WARNING: MAY BE HABIT FORMING
BELLADONNA EXTRACT (TOTAL ALKALOIDS 0.188 MG.), 15 MG

provides gentle, intermediate sedation and relaxes 'G. I.' spasm.



Butadonna quiets the "brain-on-gut" influences by providing the smooth, intermediate sedative, butabarbital sodium, desirable in combination with the proven antispasmodic, belladonna extract. Butabarbital sodium is more rapidly eliminated than phenobarbital, and avoids the latter's cumulative effect.

Indications: Antispasmodic-sedative. Useful in the treatment of peptic ulcer, gastritis, duodenitis, irritable colon syndrome, ulcerative colitis, regional enteritis, and other conditions associated with gastrointestinal spasm. Also may be useful in functional dysmenorrhea.

Usual adult dosage is one tablet 3 or 4 times daily as needed.

Caution: Contraindicated in glaucoma and urinary retention. Reduce dosage or discontinue use in event of blurring of vision, dryness of mouth, tachycardia, or excessive drowsiness. Continued use of butabarbital sodium may be habit forming.

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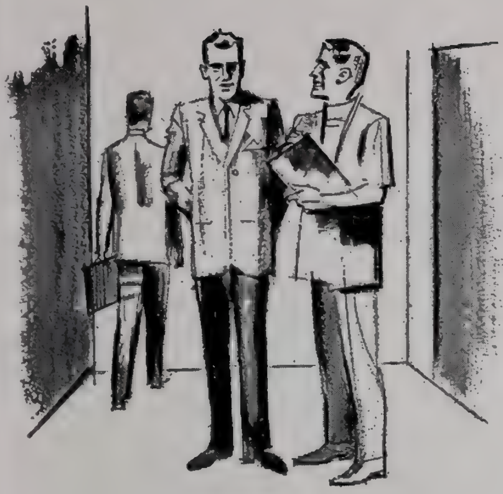

Curbstone Consultation

Ulcerative Colitis

QUESTION: Can you briefly describe the topical steroid application for ulcerative colitis, and could this be done in the doctor's office?

ANSWER: Methods of therapy depended upon anatomical involvement and degree of systemic symptoms. For ulcerative proctitis, with no or few systemic symptoms, suppositories (q.i.d.) were prescribed and the treatment was self-administered. There are several steroid suppositories on the market. For more extensive involvement, retention enemas of a suspension of hydrocortisone acetate (50 mgm.), prednisone (10 mgm.), or methylprednisalone acetate (40-120 mgm.) were prescribed and self-administered at home. For total involvement and for patients with severe symptoms, hydrocortisone sodium succinate (50-100 mgm.) was given as a proctoclysis. All methods of therapy can be used in a doctor's office, although the proctoclysis needs to be given slowly to avoid expelling, and this would tie up office space.

Only hydrocortisone sodium succinate is water-soluble. This preparation is not stable when kept in solution for several days and needs to be used promptly after mixing. The other solutions are suspensions and have to be shaken periodically, if given slowly, to prevent settling out.

Marcel Patterson, M.D.
University of Texas
Galveston, Texas

Crude Sensitivity Determination

QUESTION: In an individual who smokes excessively and has emphysema, is it necessary to do crude sensitivity determination?

ANSWER: The detrimental effects of the inhalation of the smoke of cigarettes over a period of many years is due to its destructive influence on the parenchymal tissues of the lungs, particularly of the alveoli and smaller bronchioles. Allergy or hypersensitivity to tobacco is not responsible. It is also important to remember that destructive emphysema does occur in patients who have never smoked, resulting from the allergic predisposition and long-standing bronchospasm and edema from perennial asthma, particularly due to allergy to foods.

Albert H. Rowe, M.D.
Oakland, California

I don't care how much a man talks, if he only says it in a few words.
— Josh Billings

in chronic illness

B and C vitamins are part of therapy: An imbalance of water-soluble vitamins and chronic illness often go hand in hand. STRESSCAPS capsules, containing therapeutic quantities of vitamins B and C, are formulated to meet the increased metabolic demands of patients with physiologic stress. In chronic illness, as with many stress conditions, STRESSCAPS vitamins are therapy.

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FOR PROFESSIONAL RECOMMENDATION ONLY

Each capsule contains:

Vitamin B_1 (as Thiamine Mononitrate)	10 mg
Vitamin B_2 (Riboflavin)	10 mg
Vitamin B_6 (Pyridoxine HCl)	2 mg
Vitamin B_{12} Crystalline	4 mcgm
Vitamin C (Ascorbic Acid)	300 mg
Niacinamide	100 mg
Calcium Pantothenate	20 mg

Recommended intake: Adults, 1 capsule daily, for the treatment of vitamin deficiencies. Supplied in decorative "reminder" jars of 30 and 100; bottles of 500.

LEDERLE LABORATORIES, A Division of American Cyanamid Company, Pearl River, New York

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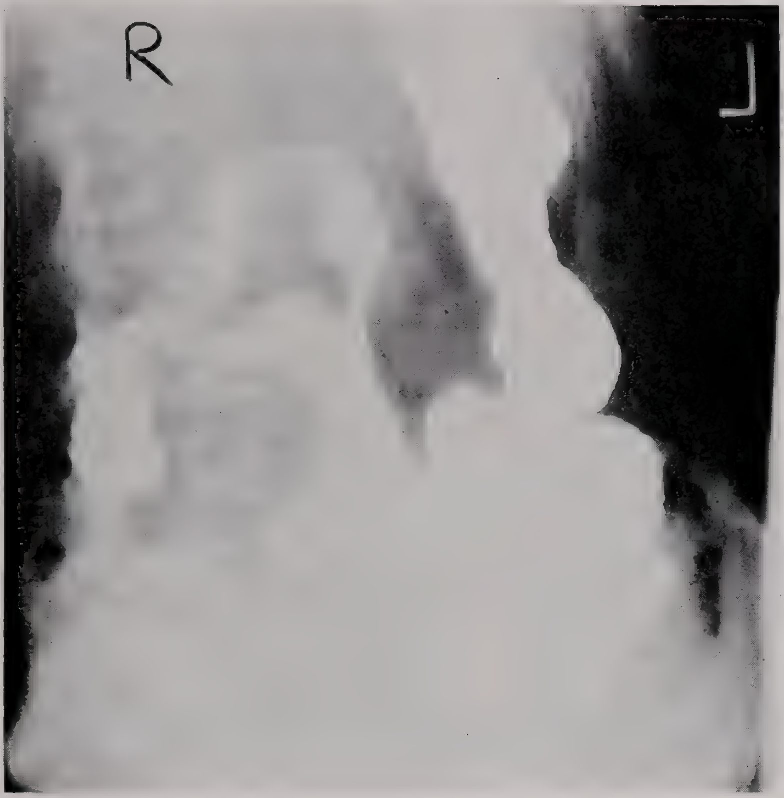
The Viewing Box



THE PATIENT is a 69-year-old female, who was first admitted to the hospital in March 1965, complaining of chronic fatigue. There was a history of ingestion of considerable quantities of aspirin. Laboratory workup at this time disclosed a hemoglobin of 7.6 grams apparently due to iron deficiency. Reticulocyte count was 2.4%. Stool guiac determinations ranged from trace to 2+. The patient had free acid. An upper gastrointestinal series was interpreted as showing a duodenal ulcer. Proctoscopic examination and x-ray examinations of the colon and small bowel were normal. The patient was treated with transfusions and an ulcer regimen with improvement. A follow-up gastrointestinal series revealed partial healing of the ulcer. The patient was maintained on the ulcer regimen and was periodically seen in the office without specific complaints. In March 1966 she was re-admitted to the hospital without subjective complaints, but with vague right upper-quadrant tenderness noted at the time of a routine physical examination. Stool guiacs had remained negative, and the hemoglobin was 12.8 grams. Repeat upper gastrointestinal examination revealed a 5 cm. mass involving the greater curvature aspect of the duodenal bulb (Figure 1). This appeared to be largely extrinsic to the lumen and to be superficially ulcerated.

Differential diagnosis was felt to be primarily that of extramucosal duodenal tumors including leiomyoma or leiomyosarcoma, aberrant pancreas, lipoma, carcinoma, carcinoid, metastasis or pancreatic invasion of the duodenum.

What is your diagnosis? (See next page.)

Diagnosis: Carcinoid of the duodenum.

At surgery a polypoid mass was found involving the greater curvature aspect of the duodenal bulb and protruding through the serosa. There were large lymph nodes encircling the porta hepatis, and nodules in both lobes of the liver. Microscopic examination revealed a carcinoid tumor extending through the entire wall of the duodenum with superficial ulceration and metastases to the liver and lymph nodes. The patient exhibited no stigmata of the carcinoid syndrome, and the 5-hydroxyindolacetic acid determination postoperatively was normal.

Carcinoids are tumors of low-grade malignancy arising from the serotonin-producing argentaffine cells found at the base of the Lieberkuhn glands of the small bowel. They fall into two general categories. Those arising in the appendix have a relatively benign course. They may metastasize to regional lymph nodes but rarely if ever metastasize distantly or give rise to the carcinoid syndrome. Extra-appendiceal carcinoids (about 40%) become progressively more rare as one moves proximally in the gastrointestinal tract. They tend to be more malignant, are often multiple, and in the approximately 15 per cent which metastasize to the liver the carcinoid syndrome is frequently seen.

C. N. Hess, M.D.*
Richard Adams, M.D.*
Minneapolis, Minnesota

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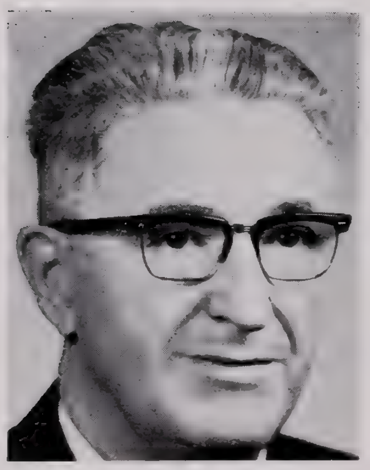
*Department of Radiology, Fairview Hospital, Minneapolis, Minnesota.

Fifty Years of Honorable Service



Dr. Lawrence J. Leonard

Dr. Leonard was born at Jordan, Minnesota, in 1893 and received his medical degree from Creighton University at Omaha, Nebraska, in 1916. He was licensed in Nebraska in 1916. After serving an internship for two years, first at St. Joseph's Hospital in St. Paul, and then at Fairview Hospital in Minneapolis, he entered the Army Medical Corps and served from 1918 to 1919 in World War I. Following his discharge, he opened a general practice in Minneapolis, with special interest in various fields, including gastrointestinal diseases and allergies. He was also interested in medical-legal problems and received a law degree in 1934 after four years of night study at the Minneapolis College of Law. He has been a member of the staffs of Fairview, St. Andrews and Glenwood Hills Hospitals in Minneapolis. Dr. Leonard has delivered over 8,100 babies, and in his spare time, plays the accordian.

Editor's Note: Because the May issue of MINNESOTA MEDICINE *was off the press at the time Dr. Lawrence J. Leonard of Minneapolis was elected to the 50 Club of the Minnesota State Medical Association, it was impossible to include his autobiography and photograph with the other newly elected 50 Club Members.*

Athletic Injuries

The Prevention and Treatment of Knee Injuries in Athletes[*]

THE TEAM physician or athletic trainer have in many instances an advantage if it can be called such, of actually seeing a knee injury occur in football. Not only do they see the accident happen but are able to observe the immediate reaction of the body to knee trauma from the instant of injury.

A trainer running onto the field in the case of a knee injury observes the injured athlete and how he is reacting to his injury. He may be holding his knee or rolling back and forth, and yet the injured leg is held very still. Because of the equipment that a football player wears we are unable to observe very much except abnormal position of the lower leg on the femur and the position of the knee in flexion or extension. We also observe the athlete himself and his reaction to pain or traumatic shock.

Our first observation of the knee injury is to decide immediately how serious it is and decide whether the athlete can walk off the field by himself, walk off on his good leg with assistance, or be carried off on a stretcher for a more complete diagnosis on the side lines or in the training room.

It is necessary that we *feel* for various signs of disability. We *feel* for any abnormal contour of the leg, the patella, dislocation of the knee joint, fractures of the patella, femur or tibia, or any abnormal bumps or depressions. A brief history of how the injury happened is valuable — not only for pertinent information but also for the opportunity it provides for distracting the athlete's attention from the pain and shock of his injury. Besides getting a brief history we try to calm the athlete, and we never tell him what type of injury he has until he is on the side lines or in the training room. The reason for this is that too many athletes are scared to death that they have a fracture or that their athletic career is at an end. We like to believe that we are treating an injured athlete rather than a knee injury; and we must consider the traumatic shock that accompanies the injury.

Along this same line we prefer that other athletes stay away as we make this preliminary diagnosis lest they make some inappropriate remark or gesture. Their remarks about getting a stretcher or calling an ambulance, or their staring at or pointing to the injury with a distressed or horrified expression or gesture does nothing to relax the tension.

If we feel the injury is severe enough we carry the athlete directly to

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[*] Presented at 113th Annual Meeting of Minnesota State Medical Association in Minneapolis, May 16, 1966.

Continued

the side lines or training room, telling him we are doing this to be able to make a more thorough examination and that we would rather he would not walk on the leg until we are absolutely sure of the severity of the injury.

When the athlete is in the training room his pants are removed even if it means cutting them off in order not to aggravate the injury; then a complete examination of the knee is made by the attending physician. The severity of the injury is evaluated at this time. If the patient isn't taken to the hospital immediately a pressure wrap is applied to the knee, the entire leg is elevated slightly, and cold packs are applied to the knee until the time it is to be x-rayed. After the x-ray the physician decides upon the best course of treatment, which may be complete bed rest, aspiration, cold packs, pressure, elevation, a cast to immobilize, or even surgery.

Treatment and Rehabilitation of Knee Injury

I have often stated that in order for a boy to be a good athlete he must be able to make his body do what he wants it to do. The athlete with a knee injury is no longer an athlete since he cannot make his body do what he wants it to do because:

1. There may be varying degrees of pain in the leg at rest and/or in motion.
2. There is a lack of full range of motion.
3. There usually is atrophy of the quadriceps and hamstrings and insufficient strength to support the injured knee.
4. The athlete does not have the proper mental attitude because he cannot do what he used to do or has a fear of re-injury.

The goal we strive for is complete or 100% rehabilitation in the shortest possible time without danger or risk of a more serious injury or a residual injury that may handicap the athlete later in life. This goal is the responsibility of the physician, the athlete, the coach, and the trainer, and they must all understand the situation and work together.

The course of treatment of the knee injury is decided by the physician, and the athlete reports to the training room for treatments. Because he may come with only an ace bandage on his knee or a half cast or even on crutches depending upon the condition of the knee, one or more of the following treatments may be used.

1. Heat — hot packs or whirlpool bath usually not until 24 to 36 hours after the injury. This type of treatment should last 20 or 30 minutes.
2. Stretching of the hamstring muscles. After preliminary heating these muscles may have to be stretched; otherwise the athlete may walk or hold his knee in the most comfortable position of 10°–20° of flexion.
3. Therapeutic exercises. These may be active, passive, assistive, progressive resistant or isometric, depending upon the need. These exercises are to restore mobility or range of motion of the knee and build strength or prevent atrophy if it hasn't already started. Straight leg raising from a supine position or exercises from a sitting position with the lower leg hanging over the edge of the table at a right angle are effective. If there is evidence of chondromalacia of the patella we prefer to start exercising the knee at 45° instead of 90° to prevent irritating the posterior aspect of the patella. To gain range of motion we use active and passive knee extension and return to starting position without

weights. To build strength and endurance we can add resistance either by a weighted boot attached to the foot or by a pulley arrangement attached to the tibia.

If surgery is performed, rehabilitation is necessary to increase the range of motion and to restore strength and endurance equal to that of the uninjured leg. The surgeon recommends postoperative exercises. During the patient's four or five day stay in the hospital he usually does straight leg raising exercises that he has been taught how to do before surgery. These are usually done for about five minutes for each hour of the day that he is awake. The methods for building strength endurance in a weakened muscle are an exact science because of the splendid work and experiments of De Lorme, Rose, Beasley, Hellebrandt and many more physicians, physiologists and physical educators.

It has been determined that the quadriceps muscle can gain or lift from five to seven pounds more weight each week by progressive resistance exercises (P.R.E.). This is done either by adding a small increment each day of 1¼ pounds or by adding the total additional weight at the beginning of each week. This should be done by a doctor's written prescription and by a physical therapist for best results.

Many athletes, especially at the high school level come to the training room each year for help with their knee problems, and the one I see most often is the athlete that has injured his knee, usually a medial collateral ligament sprain, and then rested for two or three weeks and returned to sports after the pain has gone and he or the coach thinks he is ready to play but much to his surprise the knee is re-injured.

These athletes show a definite atrophy and flabbiness of the quadriceps, and I try to impress upon them that the strength of the knee joint is determined by the strength of the quadriceps and hamstrings that are so important in its function. On knee extension they should be able to lift 75 to 100 pounds before returning to sports. Some can lift 40 or 50 pounds and feel this is enough for the quads. The hamstrings being about 60% of the strength of the quadriceps, their strength should be in the proper proportion.

In a brief summary of the vast subject of knee injury in athletes, I would like to suggest the following points:

1. An exact and complete diagnosis of the knee injury by a physician as soon as possible after the injury.
2. Written instructions or diagrams of exercises to be done by the athlete to prevent atrophy and to increase strength and endurance.
3. Always a final check of the knee by a physician before the athlete is allowed to return to sports competition. He must not be returned until he has met the following qualifications: (a.) freedom from pain. (b.) complete range of motion — active and passively, (c.) no atrophy or at least adequate strength to support the injured knee, (d.) proper mental attitude.

If he has the first three, he usually has the proper mental attitude.

Lloyd Stein*
Minneapolis, Minnesota

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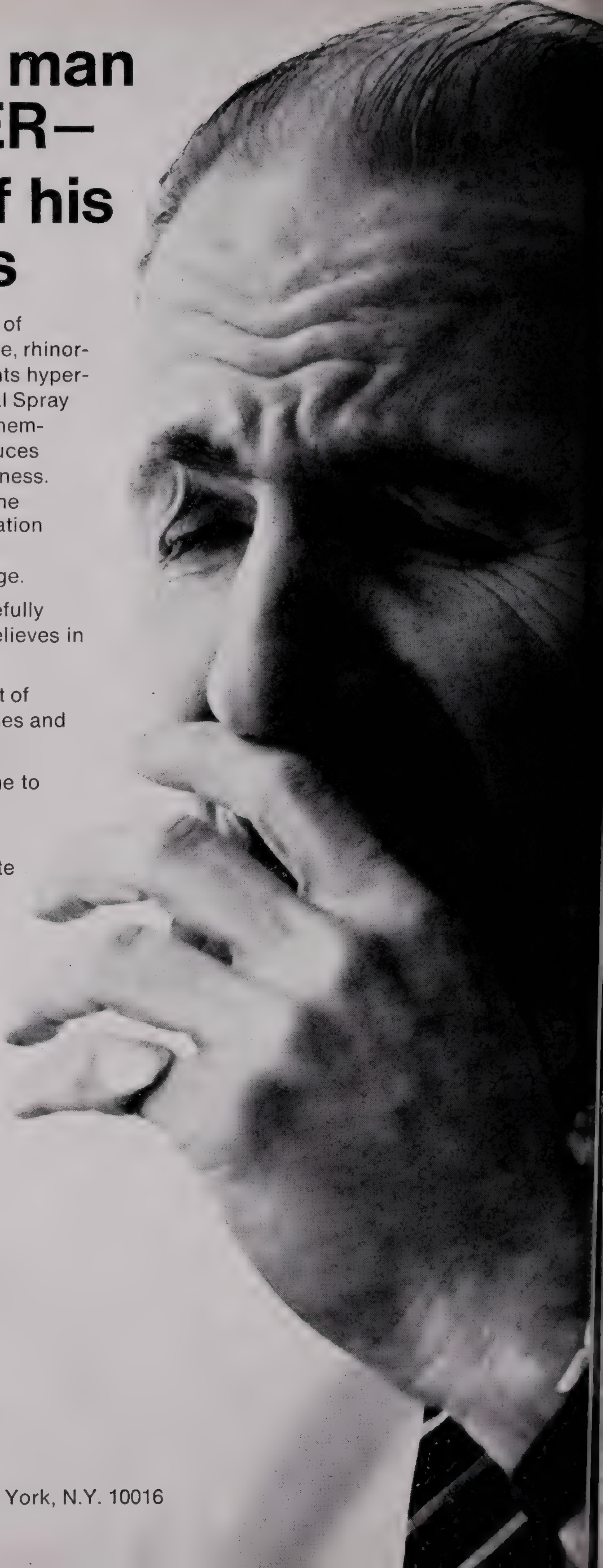
*Department of Intercollegiate Athletics, University of Minnesota.

Work is the truly indispensable vitamin. — Dorothy Canfield Fisher

Once merely a man with HAY FEVER—now a victim of his own antibodies



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Neurological Conference

Associated Problems with Parkinsonism[*]

Doctor Stanley Norman[**]

The patient is a 71-year-old white female who was seen in New Medicine Clinic for the first time on June 23, 1964, with the main complaint of a nervous stomach. Her difficulties began in early 1962, approximately one-half year after the death of her husband. She stated that she was constantly jittery, nauseated and tired. She did not enjoy being with people and had lost interest in doing anything. She did not have any plans for the future because she felt so miserable. She has had a 56-lb. weight loss during the past 2½ years. About two years ago she developed a dragging of the left foot and felt that her strength was diminishing. She then also noticed difficulty using her hands when trying to knit or sew. These symptoms have continued to the present time.

Her past medical history and review of systems were unremarkable. Her husband died 2½ years ago from aplastic anemia. The patient had spent much time caring for her husband at home and stated that she took his death very hard. Several married daughters are living nearby and visit her frequently.

Physical Findings

The physical examination revealed an asthenic, nervous, elderly lady who paced the floor during the interview. She had a mask-like facies which showed very little expression. Her blood pressure was 155/90 mm.Hg. and her pulse 92/minute and regular. There was a questionable nodule in the left lobe of the thyroid. On neurological examination the striking finding was a distinct rigidity in both upper and lower extremities. A very slight tremor of the extremities produced minimal evidence of cogwheeling on passive movement of the arms and legs. Her gait was characterized by short shuffling steps and there was a tendency to drag her left

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[*] Sponsored by the U. S. Public Health Service Grant N2502A63. These conferences are an integral part of the Comprehensive Clinic Program at the University of Minnesota Hospitals. The pediatrics conferences are held every Wednesday from 1:00 to 3:00 p.m. The adult conferences are held every Thursday at 4 p.m. Co-ordinators for the project are Dr. Charles Branthaver and Dr. Edward Defoe in Pediatrics, and Dr. Robert Soll, in Adult Neurology.

Held on May 20, 1965.

[**] Student Doctor, University of Minnesota Hospitals.

Continued

foot. Associated movements of her arms while walking were virtually absent. The deep tendon reflexes were essentially equal and no Babinski sign or clonus was apparent. Cranial nerve examination revealed an anisocoria,* the left pupil being somewhat larger than the right.

The patient's laboratory examinations all proved to be normal. These included the routine blood work, urinalysis, two-hour post-prandial blood sugar and several tests for hyperthyroidism.

Treatment and Response

Initially she had been treated with Elavil and Compazine. Eventually we added anti-Parkinson medications which included Cogentin and Artane. On this regimen she has shown some improvement, primarily in having less rigidity. Her face seems to have become more expressive, although she still has few associated movements of her arms while walking. Her depression has fluctuated throughout the course of treatment, depending to some extent on the dosage of Elavil, and she has been hostile and resistant to treatment at times. Her weight has fluctuated between 96 and 108 pounds; however, after increasing the Elavil, her weight increased to 111 pounds. Medication has not relieved her persistent nausea and her mood is still somewhat that of a depressed individual.

The Evaluation

Dr. Soll

Has the patient had a history of influenza?

Dr. Norman

No, she hasn't.

Dr. Soll

This would suggest that her parkinsonism was more arteriosclerotic than encephalitic in origin. Her age at onset of symptoms would also agree with this.

Dr. Ben Fuller**

The dragging of her left foot has been present longer than two years. Her main problem, as far as I was concerned, was not the parkinsonism, however, so much as her depression and weight loss.

Dr. Richard Magraw†

I believe she may have had two light strokes while we have been seeing her. These were in the nature of a very transient hemiparesis. The symptoms she gave seemed quite definite, although she was not confined to bed. Her most recent instance of this was three months ago if I remember correctly. Initially Dr. Fuller and I were very concerned about her weight loss. Also she has had a persistent tachycardia which remains unexplained. She presented a rather opaque and contradictory history as well as being quite opposed to any change in her therapy. Throughout our care she has presented a fog of somatic symptoms which have been quite elusive and difficult to pin down.

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*See Test Your Word Score Page 1267.

**Referring physician.

†Director, Comprehensive Clinic, University of Minnesota Hospitals.

Dr. Soll

Were you able to determine a definite date of onset of the dragging of her left foot?

Dr. Fuller

No, the patient didn't know that she was dragging her foot. Her children were the first to notice it but they didn't know when it had begun.

Dr. Soll

Her reflexes and coordination at the present time would not be consistent with any permanent residual damage characteristic of a completed stroke. She may have had a temporary cerebral ischemia; however, the lack of a definite onset and the long duration of the dragging of her left foot would not favor a transient ischemia.

Dr. John Brantner*

I wasn't able to obtain any testing immediately prior to this conference. I did talk with her and she showed this same subtle resistance. I thought that I saw the characteristic kind of prolonged grief and bereavement that one does see in some elderly people. She spoke vividly of her husband's death which was followed within a period of one year by the death of three or four of her closest friends. This showed a clear indication of depression.

Two multiphasics, one of which was done a year ago, did not show any signs of depression; however, another taken in December 1964, clearly revealed depression and anxiety. She described herself as being reasonably devout, at one time very active in church; but now she doesn't attend church anymore. I have the feeling that there is no real positive pleasure or delight in her life. Besides being bereaved over the deaths of the people she has known and loved, she is lonely, recognizes a decline in her powers, and probably fears that the daughter with whom she is living may be considering moving. She didn't talk to me about this last possibility, but I learned about it tangentially. Her daughter has received job offers from another state and has been considering them. This may be a significant factor in the patient's depression.

Dr. Soll

Depression and loss of weight are quite common in Parkinson's disease. Much of the weight loss in parkinsonism may be due to a patient's difficulty in feeding himself or swallowing. In the advanced disease many Parkinson patients are thin.

Dr. Fuller

The death of her husband was not as insurmountable for her as the death of her son-in-law. She became quite agitated at the time of his death and that is when she developed the weight loss. He was a young man, not ill at all, and fell over dead in church. After he died she never spoke of his death, and I don't know if she does yet.

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*Clinical Psychologist, University of Minnesota Hospitals.

Continued

Dr. Magraw

I would like to ascertain the actual relationship of her husband's death to her illness. If it is a matter of unresolved grief, as Dr. Brantner has pointed out, we should be able to deal with it in the ordinary way by talking with the patient — even at this point; however, she is not the usual patient in that she is a very difficult person to talk to.

Dr. Fuller

You explored the question of thyrotoxicosis, didn't you?

Dr. Magraw

Yes, very carefully, because I felt she might have an occult thyrotoxicosis manifested by tachycardia.

The protein bound iodine was 5.9 micrograms %, the radioactive iodine uptake was 30.3% in 24 hours, and the total creatinine and creatine was 0.84 grams per 24 hours.

One of the aspects of her case that prompted me to present her to this conference was the question of whether we should further investigate the possibility of cerebral vascular insufficiency by angiography. Also I would raise the possibility of using electroshock to treat her depression. She has responded to Elavil, but she is far from free of depression.

Dr. Soll

I could not detect any bruits in her carotid arteries. Significant artereosclerosis could be responsible for both the parkinsonism and the transient episodes of right hemiparesis. The absence of a carotid bruit either would suggest no involvement of the carotid circulation at all or could signify a complete occlusion of the carotid artery. But even if one were found, the age and general condition of this patient would argue against surgery. Anticoagulation would be another possible approach for treatment of an insufficiency; but this too has some serious drawbacks in view of her age, depression, and resistance to treatment.

Dr. Norman

Would vasodilators be of any benefit?

Dr. Soll

Vasodilators do not usually affect cerebral circulation significantly. Also, they may cause dilatation of other vessels in the body and thus detract from the cerebral circulation.

Dr. Fuller

What is the possibility of giving her electroshock therapy? It might be worth trying if her depression fails to respond to more conservative therapy. Are there contraindications to its use?

Dr. Magraw

Primarily the general fragility of a patient at this age.

Miss Helen Kretchmer*

I saw the patient after she had been interviewed in psychology. At that time she was already feeling weary and complained much about her nausea. I was impressed by the fact that she was good-looking and nicely dressed.

The patient and her daughter live in a pleasant neighborhood in a home that has belonged to the family for 25 years. As of now she has no difficulty in climbing stairs, but there are many steps both inside and outside the house. The family consists of four daughters, ages 30 to 45 years. The patient's three married daughters live in the same neighborhood and visit her frequently. There are several grandchildren, ages eight to 22. Although the grandchildren are busy with their own affairs and do not visit her often, she would like to see more of them.

The patient completed high school and business college, after which she worked as a secretary until her marriage at age 21. She worked long enough after 1935 to enable her to obtain Social Security coverage, which now provides her with a retirement income of $97.50 a month. The patient stated that she was still able to do housework although her hands are weak. She and her daughter maintain the house together.

Many of her interests are curtailed now because of nausea and discomfort. She had sung soprano in the church choir for many years but gave this up because of her age. She also played the piano, although her hands are not strong enough for this now. It appears that she would have ample opportunity for an adequate social life if she felt able to enter into activities. I thought a combination of factors were involved with this patient as with many older persons. She has lost her husband and her children are grown. Also she has physical and probably mental disabilities that limit her mobility, independence, and satisfactions in life. The physically-limiting problems serve to make her problem more of a reaction-depression type of situation. Like Dr. Magraw, I also felt that the family shored her up sufficiently so that she appeared more adequate than she would actually would be if left to her own devices.

The Management

Dr. Magraw

One of the complicating factors at the beginning of my contact with this patient was that it was not initially possible for me to make a diagnosis of depression. As you recall she was taking Elavil but complained that the pills made her nauseated. On the other hand, if she didn't take the pills she also became nauseated. In addition, she was also taking syrup of compazine, a medication which raised the question of a possibility of drug-induced rigidity simulating parkinsonism. But after we gradually weaned her from both medications against her will, it became clear that she had quite severe parkinsonism manifested more by rigidity than tremor. Her depression and agitation also became much more apparent after she was off Elavil. I promptly restarted these medications, and again there was a reasonable improvement. During all this time we were giving her liberal psychological support.

Initially she would not let her daughter leave the examination room;

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*Supervisor and Assistant Professor of Social Service, University of Minnesota Hospitals.

Continued

she would not even keep an appointment by herself. I really feel that she has made many unnecessary demands on her family. One of the things I would like to determine is whether there are any other means by which we can shore this woman up other than having her lean so heavily on this one particular daughter.

Miss Kretchmer

Another companion in the home who could be with the patient during the day while her daughter is gone might be helpful. This would not necessarily have to be a homemaker but someone who could come into the home for perhaps a few hours during the day, such as for part of the morning and over the lunch hour.

Dr. Magraw

We might try to work out a rotation with the three other daughters. Also, there is a girl living next door who is a trained occupational therapist. Though the patient has limitations with what she can do with her hands, this might be a possibility.

Dr. Soll

From the neurological point of view, it is very hard to be optimistic about this type of patient because Parkinson's disease usually has a steady downhill course. Although neurosurgical procedures have helped some patients with severe tremor, little benefit is obtained for the rigidity by such an approach. Surgery may alleviate the tremor temporarily, but it often will recur within months or a year or two. I think this patient is very typical of many Parkinson patients in that she is impatient and demanding. These patients hate crowds and are dependent on their families for their temperamental needs. They don't want to be bothered or irritated, yet they desire to be waited on hand and foot. It is important to discuss all these factors with the patient's family so that they will be able to understand the situation thoroughly. The family must also realize that there will be more problems as time goes on.

Miss Kretchmer

Do you think this patient will eventually require nursing home care?

Dr. Soll

I think that she very definitely may need it. Her family is able to care for her fairly well now because she can still perform much of her own self care; nevertheless, most families reach a point where they can no longer meet the demands that such a patient may place upon them. Parkinson patients eventually need almost constant care. They may become bed-ridden and develop decubitis ulcers particularly over the knees, sacrum and elbows. Very likely they will require someone to feed and bathe them. Also hot weather during the summer will present a discomforting situation for these patients and aggravate the existing problems. At the present time the patient's anti-Parkinson medication is almost maximal, and I doubt that it should be increased again, since the probability of further improvement with more medication is poor.

Dr. Fuller

One of the things that has raised the patient's spirit frequently in the past was to go swimming at the YWCA with her daughter twice a week. She thought this was great. Outside activities of this nature, if they were still possible, would increase her interests.

Dr. Brantner

Swimming is no longer associated with youth; there are programs in Saint Paul that are encouraging teaching older people, like women in their 80s, to swim. Just the other day a woman 85 years of age had just learned to swim for the first time and she was enjoying it. The elderly and rather fragile are getting a great deal of benefit from this exercise because it facilitates the release of their body from the full effect of gravity. It's pretty amazing!

The Conclusions

The following conclusions can be drawn from this conference:

1. The patient should be encouraged to participate more in activities outside her home. Swimming is particularly recommended, as well as increased social activities.
2. The possibility of additional part-time help to assist in caring for the patient should be explored. This would relieve some of the burden from the family and add a further sphere of interest for the patient.
3. The question of nursing-home care should be discussed with the family in order to prepare them for this eventuality.
4. Continued conservative care of the patient's depression can be continued for several months until it is determined whether the above steps have been beneficial. If the depression does not improve, further consideration may then be given to the use of electroshock therapy.
5. Additional increases of anti-Parkinson medication probably would provide no additional improvement in the patient's Parkinson symptoms.
6. Anticoagulation therapy or further investigation of her cerebrovascular status is not recommended at this time because of lack of substantial evidence for transient episodes of ischemia.

Robert Soll, M.D.
University of Minnesota Hospitals

Participating in the conference were Dr. John Brantner, Clinical Psychologist; Miss Helen Kretchmer, Supervisor and Assistant Professor of Social Service; Student Doctor Stanley Norman; Dr. Richard Magraw, Director Comprehensive Clinic; Dr. Ben Fuller, Referring Physician and Dr. Robert Soll, Neurologist.

Lettuce

So harmless is lettuce that it may safely be eaten raw in fevers; it allays heat, bridles choler, extinguishes thirst, excites appetite, kindly nourishes, and, above all, represses vapours, conciliates and mitigates pain, besides the effect it has upon the morals — temperance and chastity. — John Evelyn

If you have the right to complain when there is nothing to complain about, you are living in a democracy. — Banking

Democracy is built by those who live to give and destroyed by those who live to get. — Swanson Newsette

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Medical Seminar

Prenatal Care and Delivery of a Diabetic Patient

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THE DIABETIC female enjoys virtually the same statistically favorable outlook as does the nondiabetic female with regard to fertility, maternal mortality, and the incidence of spontaneous abortion. When one recalls that Eastman and Hellman[1] consider untreated diabetes and pregnancy to be basically incompatible, the importance of management of the diabetic, particularly that of the pregnant diabetic, is immediately apparent.

Kyle,[2] in 1963, compiled comparative statistics that revealed a decrease in fetal loss from a mean of 40% in series collected between 1930 and 1940, to a mean of 15% in series collected between 1950 and 1960. While fraught with the pitfalls inherent in comparative statistics, this compilation of perinatal mortality suggests marked improvement in the management of the pregnant diabetic during the past three decades. The factors held responsible by various authors for this improvement will be outlined. Management of those patients whose diabetes is of such severity as to require the use of insulin for control will be discussed.

Although the importance of many factors of management remains highly controversial, it is generally agreed that other factors have contributed substantially to improvement in both fetal and maternal welfare.

Common to virtually all programs of management of the frankly diabetic patient are (1) meticulous prenatal care, (2) delivery prior to the end of the thirty-seventh week of gestation, and (3) treatment of the newborn as premature, regardless of weight. Only the first two of these factors are within the scope of this paper.

The Team Approach

The "team approach" to management has been stressed by many authors. The reason for this emphasis is apparent when one reviews the relationship of the type of medical supervision to the perinatal death rate. As reported by Gellis and Hsia[3] and by Hagbard,[4] the perinatal mortality rate is consistently lower when the pregnant diabetic is managed by a team of physicians rather than by an individual physician. Furthermore, as a general rule, the more experienced the team, the lower the perinatal mortality rate.

The "team" is comprised of obstetrician and internist, who are joined at the appropriate times by anesthesiologist and pediatrician. Pedowitz and Shlevin[5] stressed the importance of the patient herself as a vital member of the management team.

Initial Evaluation

Ideally, every diabetic in the child-bearing age group, should, as part of her diabetic training, be made aware of the need to keep accurate menstrual records and to seek prenatal care as early as possible in the event of pregnancy. It is the responsibility of the obstetrician to convey these instructions to diabetic patients and their families when the opportunity presents itself. Furthermore, the need for such instructions should be repeatedly emphasized by the obstetrician to his medical colleagues, namely, internists, pediatricians, and general practitioners, who are most likely to deal with young diabetics.

For the diabetic, it is especially important to seek prenatal care early in pregnancy be-

Continued

cause, according to Kyle,[2] "the longer the period of supervision the greater the likelihood of a successful outcome."

At the time of the first prenatal visit, the obstetrician should, in the course of the usual history-taking and physical examination, pay particular attention to factors bearing on the estimated date of confinement. (Estimated date of confinement as used herein will mean "full term.") Accurate estimation of this date is essential because of the anticipated termination of pregnancy prior to term. The obstetrician must, throughout pregnancy, keep this date in mind and employ all necessary means to ensure accuracy of his estimate. Menstrual irregularities, common in diabetics, may make the initial estimate difficult. Therefore, a meticulous history must be taken and recorded. The patient should be given a calendar to view while trying to recall dates. Dates of intercourse, especially when relatively infrequent, may be helpful. Questions regarding factors that influence frequency and timing of intercourse such as husband's occupation, trips, illness in the family, presence of house guests, anniversaries, social events, and holidays may aid in determining the date of conception. In instances in which the date of conception can be determined, the estimated date of confinement should be calculated to occur 267 days later.

When dealing with patients who have prolonged but regular menstrual intervals, the obstetrician should recall that the preovulatory phase of the cycle is most likely to account for the prolongation. Therefore, the date of conception should be estimated as having occurred approximately 14 days prior to the expected date of menstruation, and the estimated date of confinement should be altered accordingly.

Severity of Disease

A classification of the severity of the patient's diabetes should be made because of subtle differences in management that are dependent on severity of the disease. In addition, classification will aid in the subsequent statistical comparison of the results of this management. Although numerous classifications of diabetes have been proposed, White's[6] classification has been employed most widely.

White's Classification

White's classification is based on (1) age at onset, (2) duration of diabetes, and (3) extent of any vascular and renal complications. There are six classes: *class A*, abnormal glucose tolerance test only, no insulin required, and no fasting hyperglycemia; *class B*, onset after age 20 years, duration of 0 to 9 years, and no vascular disease; *class C*, onset between age 10 and 19 years, duration of 10 to 19 years, and no vascular disease; *class D*, onset prior to age 10 years, duration of 20 years or more, and calcification in legs or retinopathy or both; *class E*, calcification of pelvic vessels; and *class F*, nephropathy.

Associated Complications

The extent of vascular complications must be determined. Retinoscopy must be performed and a careful search made for abnormalities in *renal* and *cardiac* status. Necessary laboratory studies include blood glucose value, blood urea concentration, complete blood count, chest roentgenogram, serologic test, blood type and Rh factor, urinalysis, and electrocardiogram. Kyle[2] recommends that phenolsulfonphthalein excretion be determined and notes that renal biopsy is helpful in differentiating types of renal disease. Because of the prognostic significance of calcification of pelvic, abdominal, and lower-extremity vasculature, roentgenograms of these regions are indicated in many diabetics; but such roentgenograms should not be performed during the first trimester.

Some physicians doubt that rigid diabetic control significantly alters the appearance or severity of vascular changes in diabetics. For this reason, they do not attempt rigid control based on blood-sugar levels but prefer instead "to treat the patient rather than the blood sugar." Certain laxity in metabolic control may (or may not) be acceptable in the management of the nonpregnant diabetic, but it is totally unacceptable in modern management of the pregnant diabetic.

The fetal loss associated with *acidosis or coma* or both in pregnancy is inordinately high. Kyle,[2] in a collected series, reported fetal loss of 30.1% associated with acidosis (1,039 cases) and a fetal loss of 64.5% after maternal coma (1,538 cases).

Hospitalization in Early Pregnancy

Many authors, including Eastman and Hellman,[1] Carrington,[7] and Pedowitz and Shlevin,[5] recommend hospitalization for initial studies of the pregnant diabetic. The controlled activity and diet and the ease of obtaining frequent blood- and urinary-glucose determinations enable the internist to evaluate the metabolic pattern of the individual and to make alterations in the insulin dosage schedule to fit the patient's needs. The time spent during hospitalization may also be utilized to further educate the patient in diabetic dietetics. Because nausea and vomiting may be or may soon become a problem, she should become familiar with the liquid equivalent of her prescribed caloric intake. It may also be necessary for her to review procedures for regular home-testing of urine for glucose and ketones. The final advantage of hospitalization is that it aids in impressing upon the patient the need for rigid control of her diabetes, stresses her active participation in the control program, and serves to improve her rapport with the other members of the management team.

Diet

In general, optimal gain of weight during pregnancy is the same for the diabetic as for the nondiabetic. Kyle[2] stated that, although the obese patient requires fewer calories, she should not be restricted to less than *1,200 to 1,400 calories per day* and suggested that caloric intake be based on ideal weight plus an additional 100 to 200 calories daily to meet the requirements of pregnancy.

Kyle,[2] Carrington,[7] and Pedowitz and Shlevin[5] agree that the diet should provide *1.5 to 2.0 gm. protein/kg/day.*

There is also general agreement that *50 to 75 gm. of fat* and *150 to 250 gm. of carbohydrate* are satisfactory ranges for these substances in the average diabetic diet. Disagreement exists as to whether adjustments in the dietary prescription are made best by varying the amount of carbohydrate or of fat in order to obtain the desired total calories.

Daily sodium intake should be restricted to 1.0 to 2.0 gm. throughout pregnancy.

Supplementary vitamins and iron should be prescribed as they are for the pregnant nondiabetic.

Visits

Carrington[7] recommends weekly visits to both prenatal and diabetic clinics. Kyle[2] suggests biweekly visits to the obstetrician and internist during the first half of pregnancy and weekly visits to each thereafter in order to maintain rigid diabetic control.

Should any doubt exist regarding the expected date of confinement, it would seem wise for the patient to begin weekly visits to the obstetrician by the sixteenth week if she has not done so before. Admittedly, quickening and the date of detection of the fetal heart beat are not precise measurements of fetal age. Nonetheless, these events should be determined as accurately as possible because the date of their appearance may, in combination with other observations, aid in making necessary alterations in the expected date of confinement. For the same reason, fundus height and fetal size must be carefully noted, and the obstetrician must always bear in mind the errors to which such measurements are subject. It must be remembered that the incidences of hydramnios and macrosomia are increased in diabetics but that infants born of mothers having cardiovascular-renal disease may be smaller than normal for gestational age.

Insulin

At the present time, insulin is the drug of group is more a result of the excellent diabetic, obstetric, and pediatric care provided than of the hormonal therapy employed.

Predelivery Hospitalization

Kyle[2] stated that prompt hospitalization is mandatory for such complications as mild toxemia, hydramnios, urinary-tract infection, and inadequate diabetic control. He cited evidence of decreases in uterine circulation, renal blood flow, and urinary estriol associated with activity and, therefore, believes that bed rest may result in in-

Continued

choice for the control of the deranged metabolism in the pregnant diabetic. Although considered teratogenic by some authors, this agent has been used in millions of pregnancies and has resulted in an extremely low teratogenic index. In addition, no proved preferable alternative is available at the present time.

If and when the possibilities of teratogenesis, fetal beta-cell hypertrophy, and derangements of maternal hepatic function have been eliminated, the sulfonylureas may become useful in the control of selected cases of diabetes in pregnancy.

In most instances, a dosage form of insulin having an intermediate duration of action, such as neutral protein Hagedorn (NPH), is employed as the basic replacement therapy. Its use is supplemented by the addition of regular insulin as needed to ensure rigid control. The flexibility provided by regular insulin is especially necessary early and late in pregnancy. The presence of nausea and vomiting may require use of regular insulin as the sole dosage form in early pregnancy. Flexibility in control is again essential just prior to parturition and also during the first 72 hours after delivery.

Increase Use of Insulin

As a general rule, the insulin requirement of the pregnant diabetic increases as pregnancy progresses. There is usually little or no rise during the first trimester, a gradual rise during the second trimester, and a rather abrupt rise early in the third trimester (28 to 30 weeks). From weeks 30 to 37 the insulin requirement tends to increase moderately. A gradual decrease in insulin requirement may occur for two to three weeks prior to spontaneous labor and delivery at term, but this phenomenon is rarely observed today because most pregnancies involving diabetics are terminated from two to five weeks prior to term.

It is essential to realize that the above pattern of increased insulin requirements applies generally and that many exceptions occur. Jones[8] and Pedersen[9] reported that only about two thirds of their pregnant diabetics required increased insulin dosage, whereas in one fourth the requirement was unchanged, and in one tenth the requirement actually decreased during pregnancy. It is, therefore, evident that the changes in insulin dosage during pregnancy cannot be predicted for the individual patient and that frequent blood-sugar determinations are essential for maintenance of excellent control.

Decrease Insulin Requirement

Two additional observations deserve consideration: (1) A decrease in insulin requirement that occurs only during hospitalization should arouse suspicion that the patient is not adhering to her prescribed diet while at home; and (2) an abrupt decrease in insulin requirement usually is cause for concern of fetal welfare and calls for rapid reassessment of fetal and maternal status so that appropriate action based on the results of this reassessment can be taken.

Altered Renal Threshold

Alterations in the renal threshold for glucose plus the presence of additional reducing substances in the urine during pregnancy deserve discussion because various tests of urinary-reducing substances provide the patient with guidelines in determining alterations in insulin dosage on a day-to-day basis. It is, therefore, important to inform the patient that when she uses urine testing as a dosage guideline any given degree of glycosuria will, as a general rule, require the addition of a smaller amount of insulin than was the case prior to her pregnancy.

Daily Clinical Testing

Because the renal threshold for glucose occasionally increases during pregnancy and because the degree and onset of lactosuria is so variable, simultaneous determination of blood and urinary glucose on several occasions during pregnancy may prove useful in management. In addition, the physician should realize that the "stick" tests (Tes-Tape, Clinistix, Uristix, and the like) are semiquantitative glucose oxidase tests, whereas the Clinitest tablet is a modified Benedict copper-reduction test. The Clinitest tablet, while providing more quantitative measurement of reducing substances, is not specific for glucose.

Ketonuria

Most authors recommend daily testing of fractional urines for both glucose and acetones. Pedowitz and Shlevin[5] stress the need for the patient to report any persistent or progressive ketonuria. This is understandable in view of the previously mentioned effect of acidosis and coma on the perinatal mortality. Conversely, hypoglycemia, according to Kyle,[2] does not seem to affect fetal survival adversely. He suggests that this finding may be accounted for by the relative impermeability of the placenta to insulin, by the remarkable tolerance of the fetus to hypoglycemia, by the capacity of the fetal liver to respond to hypoglycemia, or by a combination of these factors.

Blood Glucose

To determine necessary changes in insulin requirements, Carrington[7] employs fasting blood-glucose values. Kyle[2] and several other authors prefer to base insulin requirements on the 2-hour postprandial true glucose values and attempt to maintain this level at 120 mg. per 100 ml. of blood or less. Kyle suggests that this determination be made at each visit. In addition, he suggests that a 24-hour quantitative glucose determination be made at frequent intervals and an attempt be made to limit glycosuria to 5 to 10% of the available carbohydrate intake. When a daily urinary loss of 20 gm. or more of glucose is observed in the absence of hyperglycemia, he suggests a dietary supplement that corresponds to the amount of carbohydrate lost.

Although it is true that several authors have reported no correlation between fetal survival and maternal blood-glucose levels per se, it is also true that the management program of Given and associates,[10] which allows only symptomatic control while employing management otherwise similar to that practiced by most teams, resulted in a fetal loss of 20% in viable infants of diabetic mothers. Furthermore, many authors have reported a lower incidence of large infants born to diabetic mothers in whom chemical, rather than symptomatic, control was maintained.

Diuretics

If salt restriction alone proves inadequate in controlling edema, diuretics should be used. Chlorothiazide and hydrochlorothiazide have the advantage of having proved their therapeutic effectiveness. Carrington[7] recommends that thiazides or ammonium chloride be given for three-day periods, with a three-day omission of drug administration between each period. Driscoll and Gillespie[11] use up to 200 mg. of hydrocholorothiazide daily (divided doses), and, if necessary, give 2-ml. injections of meralluride (Mercuhydrin) once or twice weekly. With the thiazides, supplementary use of potassium may be necessary and electrolyte levels should be checked frequently. The reported hyperglycemic effect of thiazide derivatives has not proved a significant problem in maintaining rigid control of the diabetes.

The effect of diuretics on the severity of hydramnios is controversial. White[12] believed that the use of diuretics decreases the severity, but not the incidence of this complication — which is increased in diabetics.

Hormonal Therapy

The use of estrogens and progestins as adjunctive therapy remains highly controversial. The Joslin Clinic group has employed hormonal therapy extensively and reported a perinatal mortality rate of 9[11] to 13%[13] when hormonal therapy was employed as part of the diabetic management program. The main argument against its use is that comparable perinatal mortality rates are attained by others who do not employ hormonal therapy. In fairness to White and her group, it should be pointed out that the Joslin Clinic group has included in their series a much higher proportion of severe diabetics than have the other groups. White has stated the belief that her program of hormonal therapy reduces that incidence of spontaneous abortion, premature labor, toxemia, and severe hydramnios.

It is a widely held belief that the enviable fetal salvage attained by the Joslin Clinic

Continued

creased fetal survival. Driscoll and Gillespie[11] stressed restriction of activity for patients with renal disease.

Timing of Delivery

Timing of delivery is one of the most important, and often the most difficult, of the obstetric decisions in the management of the frankly diabetic patient.

Prior to Term

There is general agreement that these patients should be delivered prior to term. However, there is disagreement and literary confusion regarding the specific optimal time for delivery of the well-controlled, frank diabetic who is free from other complications. Some authors[3,4,7] have recommended delivery from the thirty-fifth through the thirty-seventh week, whereas others[5,14] have suggested 18 to 24 days prior to term. Driscoll and Gillespie[11] stated time of delivery more specifically according to classification: by the end of the thirty-seventh week for class B; between the thirty-sixth and thirty-seventh weeks for class C; and individualization for classes D and E since a favorable prognosis for this group is poor after the thirty-sixth week.

It must be stressed that, in any decision regarding the date of delivery for the individual patient, many factors other than the above-mentioned range of dates must be considered, because these guidelines simply represent the period in gestation in which various authors have obtained greatest salvage. Therefore, timing of delivery per se cannot be held solely responsible for the fetal salvage attained during the above-mentioned periods.

Choice of Delivery Date

Since various authors have reported fetal salvage of from 82 to 92% when using preferred dates of delivery that have ranged from approximately 18 to 35 days prior to the expected date of confinement, it would seem wise to anticipate delivery of the individual patient during this period. The choice of the *exact* date should be determined after full evaluation of the following factors.

1. Delivery prior to the thirty-second week is accompanied by a neonatal loss of more than 50% because of prematurity.[3]

2. Postponement of delivery until after the thirty-seventh week will result in a stillbirth loss in excess of 25%.[3]

3. The degree of diabetic control after repeated bouts of ketoacidosis is associated with an increased incidence of perinatal death. The presence of recurrent ketoacidosis should influence one to advance the date of delivery.

4. Presence and severity of complications should be considered. Kyle[2] stated that "although toxemia is generally accepted as an indication for prompt interruption in the thirty-fifth week, Given . . . does not temporize even at the thirty-fourth week." Similarly, marked hydramnios is considered by many to be an indication for early delivery. The presence of progressive renal failure or advancing retinitis influences one to deliver early. Purely obstetric indications — such as third trimester bleeding — may occur, and these must be individually evaluated and managed according to sound obstetric judgement.

5. Fetal size and age should be considered. The entire discussion of timing of delivery assumes that fetal age is known. Such an assumption is necessary but is risky, as virtually all large series mention instances in which errors were made in determining fetal age — often with disastrous consequences. Errors are made in both directions, that of over-estimating fetal age seemingly being the more common and, of course, leading to the delivery of "too premature" infants. It is for this reason that the obstetrician must, from the time of the initial history and physical examination until delivery, secure and record every possible bit of information that may aid in accurately determining fetal age. Means of arriving at this determination have been stressed previously. Although its value has been questioned, a lateral abdominal roentgenogram that shows ossification centers in the distal femoral epiphyses is comforting to most obstetricians. In addition, congenital abnormalities that might influence the mode of delivery are occasion-

ally discovered. Failure to visualize the epiphysis does not unequivocably prove immaturity.

Good correlation has been reported between fetal survival and birth weights between six and eight pounds in infants of diabetic mothers. In any attempt to deliver infants of this size, the presence of a small fetus in the absence of evidence of placental insufficiency indicates relatively later delivery. Excessive fetal size indicates relatively earlier delivery.

6. Previous obstetric history would seem to be of relatively less importance than most other considerations — especially if diabetic control in the present pregnancy has been good.

7. Determinations of estriol in the urine may become a valuable aid in determining the date of delivery. Greene and Touchstone[15] reported the results of urinary-estriol excretion in 35 pregnant diabetics. Of the 35 patients, 10 had 24-hour urinary excretion of estriol determined daily, seven had such determinations done three times weekly, eight had them done once weekly, and 10 patients had single determinations made. For 19 of the patients the 24-hour urinary-estriol excretion was more than 12.0 mg. and no perinatal difficulty was encountered. Of the remaining 16 patients, four with perinatal difficulties had levels below 4.0 mg. per 24 hours and their infants died, whereas 12 had levels between 4.0 and 12.0 mg. per 24 hours and their infants survived.

Value of Estriol Determination

Serial urinary-estriol determinations appear to be of particular value in cases of suspected placental insufficiency. Such determinations may prove useful in cases in which, for various reasons, the obstetrician encounters unusual difficulty in weighing the risks of fetal jeopardy in utero against those of infant prematurity.

In an assessment of significance of urinary-estriol levels, the following should be remembered: (1) The levels are not a reliable index of placental function in cases of erythroblastosis;[11] (2) acute urinary-tract infection, especially pyelonephritis, is accompanied by low estriol levels;[16] (3) mandelamine may render estriol undetectable by some laboratory methods;[15] and (4) the glucuronidase method, rather than the acid-hydrolysis method, of urinary estriol determination should be used for diabetics because of a tendency toward falsely low values reported in urine that contains glucose when the latter method is used.[16]

Mode of Delivery

Although labor may begin spontaneously, usually the obstetrician must choose between cesarean section and induction of labor in terminating the pregnancy. If induction is chosen, it may be either medical or surgical or a combination of both. In any event, the physician must decide the circumstances under which he will interrupt either spontaneous or induced labor by cesarean section.

Induced Trial

In discussing induction of labor, Driscoll and Gillespie[11] have stated, "In all instances it is necessary that productive labor ensue within six hours following amniotomy and/or oxytocin induction. After a maximum of eight to ten hours of labor, delivery should be imminent and an easy low forceps delivery anticipated."

Cesarean Section

They consider cesarean section to be indicated when the above criteria are not fulfilled. In addition, they consider previous cesarean section, previous difficult pelvic delivery, fetal distress, abnormal presentation (including breech), and E and F classifications as indications for section.

The analysis by Gellis and Hsia[3] of the relationship of mode of delivery and perinatal mortality indicates that good results may generally be obtained by either the abdominal or vaginal route when proper indications for each method of delivery are observed. Different authors have different opinions as to what may consititute these "proper indications."

Vaginal Delivery

In general, vaginal delivery is reserved for well-controlled diabetics who have minimal or no other complications, in whom the vertex presents and no disproportion exists,

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and in whom an "atraumatic," reasonably rapid, uncomplicated delivery may be expected.

Also in general, best results seem to be obtained when indications for induction are strict and those for cesarean section are liberal.

Prolonged labor or traumatic delivery (or both) is tolerated very poorly by infants of diabetic mothers. Midforceps and breech deliveries are accompanied by excessive neonatal morality, and mortality rates in excess of 70% have been reported in breech delivery of viable infants.

Predelivery Management

Predelivery hospitalization has been previously mentioned.

Insulin

Each internist seems to have his own dosage schedule of insulin for the immediate pre-partum and postpartum periods. Some employ only regular insulin during this period, whereas others prefer partial replacement with NPH or Lente and employ regular insulin for fine adjustments. Most give a reduced dose of insulin on the day of delivery, the reduction usually being greater in patients slated for section than in those for whom vaginal delivery is planned. A postpartum decrease in insulin requirement is anticipated. In most instances a return to insulin requirements that were used before delivery is expected, but requirements may prove to be greater or less than prepregnancy requirements.

Anesthesia and Analgesia

In deciding on premedication and type of anesthesia both obstetrician and anesthesiologist must keep in mind the need to regard the fetus as premature regardless of size or weight.

A parasympatholytic drug such as atropine in a 0.4-mg. dose should be given about one hour prior to anticipated delivery.

Analgesic agents should not be used prior to elective cesarean section, and dosage should be kept to a minimum if such agents are used prior to vaginal delivery. Hartridge[17] recommends that only small dosages be used when narcotics are necessary. She recommends 50 mg. of meperidine (Demerol) or 30 mg. of alphaprodine (Nisentil) and states that nalorphine (Nalline) or levallorphan tartrate (Lorfan) should be given 15 to 20 minutes prior to delivery if the above narcotics have been given less than two hours prior to delivery.

The use of local field block for cesarean section and pudendal block for vaginal delivery theoretically results in the least possible disturbance of fetal physiology. However, in the hands of skilled anesthesiologists, spinal, caudal, or general anesthesia has been employed and the results have been statistically comparable.

Summary

Management factors responsible for improved maternal and perinatal mortality in cases of coexistent diabetes and pregnancy have been discussed and the importance of the following factors stressed: (1) meticulous prenatal care by an experienced team that includes obstetrician, internist, pediatrician, and patient; (2) rigid chemical control of the diabetes beginning early in pregnancy; (3) frequent prenatal visits for early recognition and aggressive treatment of complications; (4) control of fluid balance to decrease the incidence of toxemia and degree of hydramnios; (5) ante-partum hospitalization; (6) delivery from 18 to 35 days prior to term; and (7) treatment of the newborn as premature regardless of weight.

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4-17 May be secured from the author or the reprints.

Grand Rounds

Primary Aldosteronism

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SINCE 1954 and Conn's description of a case of aldosterone excess caused by an autogenously functioning tumor of the adrenal cortex,[1] primary aldosteronism has been a recognized, curable cause of hypertension. During the intervening years aldosterone excess has been demonstrated in a variety of clinical entities, including edematous states, sodium deficiency syndrome, and cases of hypertension in which no adrenal tumor was demonstrable. Thus, some confusion about the significance of aldosterone excess arose and probably dampened the clinician's interest in searching for cases of primary aldosteronism.

However, with clarification of the renin-angiotensin-aldosterone regulatory mechanism, it now appears to be possible to separate these clinical entities.[2] Indeed, it is through measurement of renin levels that Conn has described subclinical cases of primary aldosteronism[3] and has suggested that this condition may be present in 20 per cent or more of hypertensive patients.[4,5] This interesting and provocative suggestion has prompted new interest in this syndrome.

The purpose of this paper is to outline the present concepts of the renin-angiotensin-aldosterone system by briefly reviewing the data which led to its description as a physiologic regulatory mechanism. Finally, the syndrome of primary aldosteronism, its possible prevalence, and diagnostic considerations will be discussed.

Renin-Angiotensin

Renin, an active principle in crude kidney extract, which will produce hypertension, has been known since the turn of the century.[6] It was

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*Medical Grand Rounds, Hennepin County General Hospital, March 1, 1966.

Continued

shown by Page and Helmer along with Houssay and Braun-Merendez that renin is a proteolytic enzyme which acts upon a plasma precursor to yield a potent vasopressor.[7] There is good evidence that renin is produced by cells in the juxtaglomerular apparatus of the kidney.[8] Renin converts angiotensinogen (an alpha-2-globulin produced in the liver) to angiotensin I, a decapeptide. Angiotensin I is converted by an enzyme present in the plasma to angiotensin II, an octapeptide.[9] Angiotensin II is a very potent vasopressor and was at one time thought to have sodium-retaining properties. It should be understood that any action ascribed to renin is actually mediated through angiotensin II.

Aldosterone

Desoxycorticosterone, the life-saving factor for the Addisonian, was synthesized by Reichstein in 1938. The search for the naturally occurring sodium-retaining steroid of the adrenal cortex culminated in 1954 when Simpson, Tait, Reichstein, Wettstein and Nehrer isolated 18-oxo-corticosterone, later named aldosterone.[6] Desoxycorticosterone and aldosterone both[10] increase the exchange of potassium for sodium in the distal renal tubule, the sweat glands, and the salivary glands. An excess of either of these substances will produce sodium retention to such an extent that plasma volume increases, potassium deficiency and alkalosis ensue, and hypertension develops.[6] A steroid analogue of these hormones, spironolactone, will competitively inhibit the action of both desoxycorticosterone and aldosterone.[11]

Aldosterone is formed and secreted by the zona glomerulosa of the adrenal cortex, a process which goes on in the absence of ACTH.[6] The average man on a normal sodium intake will secrete between 40 and 180 micrograms of aldosterone during a twenty-four hour period. Because the half-life of the hormone is only 35 to 50 minutes, circulating levels are in the range of 0.01 micrograms per 100 ml. Aldosterone is metabolized by the liver and 90 per cent is excreted as the glucuronide of tetrahydroaldosterone. The remainder is excreted as conjugated 3-oxo-aldosterone and a tiny fraction as free aldosterone. It is the latter 10 per cent that is measured chemically; therefore, twenty-four hour urinary aldosterone levels are reported as ranging from 5 to 15 micrograms.

Renin-Angiotensin-Aldosterone System

Search for the regulatory mechanism of both aldosterone and renin drew these two substances together. Acute hemorrhage, which had been known to produce elevated renin levels, was found to be a most potent stimulus to aldosterone secretion. Similarly, constriction of the inferior vena cava, sodium depletion, constriction of the renal artery, and even the upright position in man were all shown to produce elevation of both renin and aldosterone levels.[2,12] The granularity of the juxtaglomerular cells (indicative of renin content) was shown to be increased in Addison's disease and decreased following injections of desoxycorticosterone.[8] Administration of renin, on the other hand, will produce hypertrophy of the zona glomerulosa of the adrenal gland and a graded response in aldosterone secretion in man.[13] Moreover, non-pressor levels of infused angiotensin II will cause increased secretion of aldosterone. The nephrectomized animal has low basal levels of aldosterone and will not respond to acute hemorrhage with increased aldosterone levels,[14] and the apparent sodium-retaining effect of angiotensin II is absent in the adrenalectomized animal.[14,17,18] All these observations led to the conclusion that angiotensin II is the aldosterone-stimulating hormone and that its regulation is dependent upon renin secretion. At present it is not possible to say whether renin secretion is regulated by blood volume, sodium concentration, or both.

At any rate, the system, as schematized in Figure 1, is thought to operate in the following manner. The juxtaglomerular apparatus of the afferent renal arteriole contains "stretch" receptors (or possibly a sodium-load chemoreceptor). The stimulus for renin release from the granules in these cells is a decrease in plasma volume (or sodium concentration) which causes a decrease in "stretch." The released renin then converts angiotensinogen to angiotensin I, which is subsequently converted to angiotensin II. Angiotensin II stimulates the zona glomerulosa of the adrenal cortex to secrete aldosterone. Aldosterone acts upon the distal renal tubule, the sweat glands, and the salivary glands to conserve sodium by enhancing the potassium sodium exchange mechanism. Water is reabsorbed along with the sodium, the plasma volume increases, "stretch" on the receptors then increases, and the stimulus for renin release is shut off.[19]

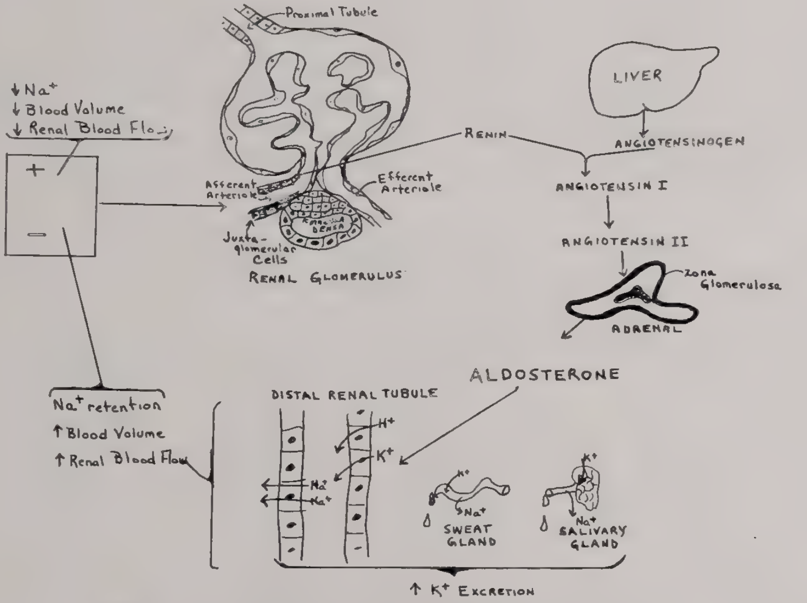

Proximal Tubule
↓ Na+
↓ Blood Volume
↓ Renal Blood Flow
+
−
Afferent Arteriole
Efferent Arteriole
Macula Densa
Juxta-glomerular Cells
RENAL GLOMERULUS
RENIN
LIVER
ANGIOTENSINOGEN
ANGIOTENSIN I
ANGIOTENSIN II
Zona Glomerulosa
ADRENAL
ALDOSTERONE
Na+ retention
↑ Blood Volume
↑ Renal Blood Flow
DISTAL RENAL TUBULE
H+
K+
Na+
Na+
K+
Na+
SWEAT GLAND
K+
Na+
SALIVARY GLAND
↑ K+ EXCRETION

Fig. 1 — Renin-Angiotensin-Aldosterone System.

Physiologic Considerations

The observation of the above system as a physiologic mechanism was first noted by Conn in his study of the acclimatization of man to a warm climate. Large volumes of sodium-rich sweat are lost, and the individual becomes readily fatigued secondary to his sodium and water depletion. However, over a period of 10 to 20 days he is able to regain his sodium balance, even though he is still perspiring. This comes about through an elevation of the aldosterone level and a marked drop in the sodium content of the urine, sweat and saliva. Moreover, the plasma volume is

Continued

increased, and this is probably necessary for increased perfusion of the skin to occur. A very interesting, but as yet unexplained phenomenon occurs in these individuals, as well as in individuals given exogenous desoxycorticosterone or aldosterone.[10,20] This phenomenon, known as "renal escape," is that the effect of aldosterone on conservation of sodium becomes inoperable in the kidney while still operating on the sweat and salivary glands. It is indeed fortunate that this occurs, since the kidney can initially retain large amounts of sodium in the event of an acute shortage, but can then return to handling an excess of sodium when a new equilibrium has been established.

Similarly, persons fed a low sodium diet will show increased aldosterone levels. It was mentioned previously that the upright position caused an elevation of both renin and aldosterone levels; so the recumbent position causes a decrease in aldosterone and renin levels. The explanation for these postural differences is that the effective blood volume is increased in recumbency and decreased in the upright position.

Pathology

One can visualize from the above description of the system several ways in which the mechanism can be kept in operation. One would be a constant low plasma volume or sodium level, a second, a constant elevation of renin levels, and a third, constant elevation of aldosterone levels. It is on this basis that the syndromes of excessive aldosterone secretion will be dealt with. The first and second states will be considered as secondary aldosteronism, and the third state as primary aldosteronism (Table 1). Such a condition occurs in the edematous states of nephrosis, cardiac

TABLE I**

Possible Combinations of Elevated and Depressed Levels of Aldosterone Secretion and Plasma Renin Activity

	Renin Activity			
Renin Activity	↓	↓	↑	↑
Aldosterone Secretion	↑	↓	↓	↑
Clinical Conditions	Primary Aldosteronism (tumor)* Administration of Exogenous Aldosterone +	Salt, loading* Dexoxycorticosterone plus salt* Plasma volume expanders+ Inappropriate secretion of ADH +	Primary Aldosteronopena + Deficiency of 18-hydroxycorticosterone dehydrogenase + (Ulick) Addison's disease* Salt-losing congenital adrenal hyperplasia + Idiopathic postural hypotension + Glycyrrhizate*	Salt restriction* Diuretics* Salt-losing pyelonephritis + Juxtaglomerula hyperplasia and aldosteronism* (Bartter) Malignant Hypertension* Hemorrhage* Edematous states: Congestive heart failure* Hepatic cirrhosis* Nephrosis* Pregnancy* Diabetes Insipidus +

*Combination demonstrated.
+Renin values not reported.

From Conn: JAMA 190:219, 1964.

Constant Low Plasma Volume or Sodium Level

The excess aldosterone secretion due to a constant low blood volume or low sodium concentration can be considered as a compensatory mechanism.

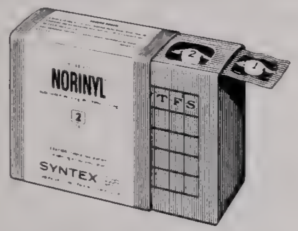
plus important supportive benefits that help her through those critical early months of oral contraception

low incidence of side effects

Low incidence of BTB and spotting, nausea and amenorrhea tends to minimize side effect problems and increases patient cooperation.

no confusion about dosage

An unbreakable "confusionproof" package makes it easy to adhere to prescribed dosage schedule: individually sealed tablets numbered from 1 through 20 *plus* monthly calendar record enables patient to double-check dosage intake by day and corresponding tablet number.



Contraindications: Thrombophlebitis or pulmonary embolism (current or past). Existing evidence does not support a causal relationship between use of Norinyl and development of thromboembolism. While a study which was conducted does not resolve definitively the possible etiologic relationship between progestational agents and intravascular clotting, it tends to confirm the findings of the Ad Hoc Advisory Committee appointed by the Food and Drug Administration to review this possibility. Cardiac, renal or hepatic dysfunction. Carcinoma of the breast or genital tract. Patients with a history of psychic depression should be carefully studied and the drug discontinued if depression recurs to marked degree. Patients with a history of cerebral vascular accident.

Warning: Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Precautions: By May 1963, experience with norethindrone 2 mg.—mestranol 0.1 mg. had extended over 24 months. Through miscalculation, omission or error in taking the recommended dosage of Norinyl, pregnancy may result. If regular menses fail to appear and treatment schedule has not been adhered to, or if patient misses two menstrual periods, possibility of pregnancy should be resolved before resuming Norinyl. If pregnancy is established, Norinyl should be discontinued during period of gestation since virilization of the female fetus has been reported with oral use of progestational agents or estrogen. When lactation is desired, withhold Norinyl until nursing needs are established. Existing uterine fibroids may increase in size. In metabolic or endocrine disorders, careful clinical preevaluation is indicated. A few patients without evidence of hyperthyroidism had elevated serum protein-bound iodine levels, which in the light of present knowledge, does not necessarily imply hyperthyroidism. Protein-bound iodine increased following estrogen administration. Bromsulphalein retention has occurred in up to 25% of patients without evidence of hepatic dysfunction. Studies from 24-hour urine collections have shown an increase in aldosterone and 17-ketosteroids and decrease in 17-hydroxycorticoid levels. Thus, Norinyl should be discontinued prior to and during thyroid, liver or adrenal function tests. Because progestational agents may cause fluid retention, conditions such as epilepsy, migraine and asthma require careful observation. Thus far no deleterious effect on pituitary, ovarian or adrenal function has been noted; however, long-range possible effect on these and other organs must await more prolonged observation. Norinyl should be used with caution in patients with bone, renal or any disease involving calcium or phosphorus metabolism.

Side Effects: Intermenstrual bleeding; amenorrhea; symptoms resembling early pregnancy, such as nausea, breast engorgement or enlargement, chloasma and minor degree of fluid retention (if these should occur and patient has not strictly adhered to medication plan, she should be tested for pregnancy); weight gain; subjective complaints such as headache, dizziness, nervousness, irritability; in a few patients libido was increased. In a total of 3,090 patients, 2.2% discontinued medication because of nausea.

NOTE: See sections on contraindications and precautions for possible side effects on other organ systems.

Dosage and Administration: One Norinyl tablet orally for 20 days, commencing on day 5 through and including day 24 of the menstrual cycle. (Day 1 is the first day of menstrual bleeding.)

Availability: Dispensers of 20 and 60 tablets; bottles of 100.

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failure, cirrhosis and idiopathic edema. Although the major problem in these conditions is sodium and water retention, the actual intravascular volume is low and therefore acts as a stimulus for renin release and aldosterone secretion. An additional factor in right heart failure, and especially in cirrhosis, is a decreased rate of metabolism of aldosterone by the liver, whereby further elevation of aldosterone levels occurs. Hence the body is stimulated to conserve more sodium and more water, which escapes into the extravascular space, and a "vicious circle" ensues. Probably the reason that hypertonic saline sometimes produces a diuresis in these patients is that aldosterone production is shut off by this maneuver.

Salt restriction, salt-losing nephritis, diabetes insipidus, and salt-depleting diuretics will all produce an elevation of aldosterone.

Elevation of Renin

The condition of overproduction of renin will be considered as primarily pathologic. This occurs in renal hypertension, whether on the basis of renal artery stenosis or renal arteriolar constriction. Actually, this could be considered a localized decrease in blood volume to the juxtaglomerular apparatus.[2] Renin levels are elevated in Addison's disease, if untreated with mineralocorticoids, but do not produce hypertension under these circumstances. The elevated renin levels of renal hypertension do produce secondary aldosteronism, however, and it is this category of patients that presents the greatest problem in the differential diagnosis of primary aldosteronism.

Elevation of Aldosterone

Primary aldosteronism is caused by the autogenous secretion of aldosterone from an adrenal cortical adenoma. Because of this the blood volume should be expanded, the serum sodium level normal or increased, and the stimulus for renin release absent; therefore renin levels should be low.

Recognition of the syndrome of mineralo-corticoid excess in its flagrant form with hypertension, hypernatremia, hypokalemic alkalosis, increased urinary potassium, and the clinical symptoms of headache, malaise, polyuria, polydipsia, and muscle weakness should not be difficult and can readily be confirmed by an elevated urinary aldosterone level.[21] This does not, however, differentiate primary from secondary aldosteronism of renal origin. It has been proposed that an evaluation of the plasma volume will make this differentiation, but the overlap of results in these two syndromes is enough to warrant a better method.[22,23]

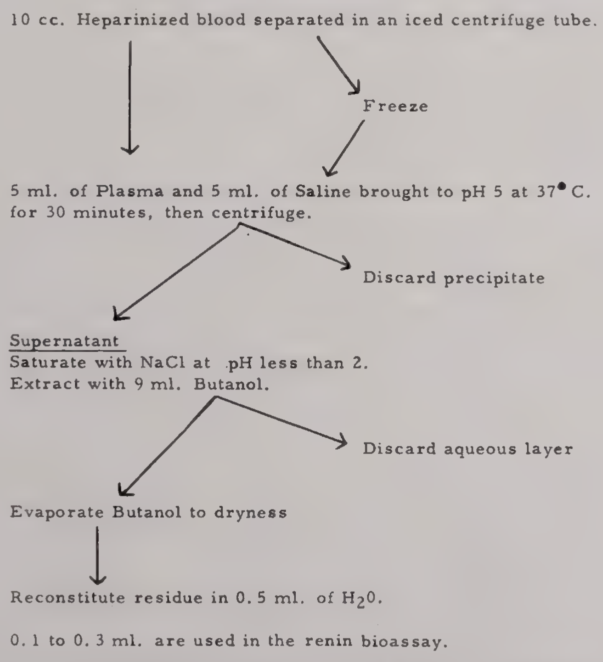
Conn, using the reasoning given above, suggested that the real differentiation between these two syndromes could be made on the basis of renin level determinations. Even though others had reported renin levels of patients with primary aldosteronism to be normal,[24] Conn pointed out that the most reliable test for renin levels that were low on the basis of suppression by an autogenous tumor would be to do the assay under conditions of maximal stimulation for renin secretion. By keeping patients on a sodium intake of 10 milliequivalents per day for several days, and then obtaining a blood sample after they had been in an upright position for at least four hours, Conn was able to separate clearly the normals from the patients with primary aldosteronism.[2]

Having proved the usefulness of the observation of increased aldosterone levels accompanied by decreased renin levels in the diagnosis of primary aldosteronism, Conn then suggested that hypertensive individuals with aldosterone-secreting tumors must go through the stages of the acclimatized man. In other words, hypertensives, on a good potassium intake and manifesting the "renal escape" phenomenon, must not only exist, but were probably labeled as essential hypertensives, were put on a low sodium diet, and had their aldosterone-secreting adenomas masked for years.[4] In 1965 he reported just such a case.[3]

Theoretical Considerations

Because the adenomas removed from patients with primary aldosteronism are indistinguishable from the benign adrenal cortical adenoma found at autopsy, and because he had proven to his own satisfaction that normokalemic primary aldosteronism exists as a curable cause of hypertension, Conn has suggested that 20 to 25 per cent of persons with so-called essential hypertension actually have aldosterone-secreting adenomas of the adrenal cortex. His reasoning is based on the review of several autopsy studies. In 1945 Russi reported a series of 9,000 autopsy cases in which the incidence of adrenal cortical adenoma was 3.7 per cent. The incidence of hypertension in this series was 14 per cent; but 73 per cent of the adenomas were in the hypertensive group. In other words, 19 per cent of the hypertensives had adrenal cortical adenomas.[5] Then, comparing a matched group of 220 hypertensives with 220 non-hypertensives, 1.8 per cent of the non-hypertensives and 20 per cent of the hypertensives had adrenal cortical adenomas at autopsy. Similarly, in a group of 97 hypertensives

TABLE 2*
Renin Measurement



10 cc. Heparinized blood separated in an iced centrifuge tube.

Freeze

5 ml. of Plasma and 5 ml. of Saline brought to pH 5 at 37° C. for 30 minutes, then centrifuge.

Discard precipitate

Supernatant
Saturate with NaCl at pH less than 2.
Extract with 9 ml. Butanol.

Discard aqueous layer

Evaporate Butanol to dryness

Reconstitute residue in 0.5 ml. of H_2O.

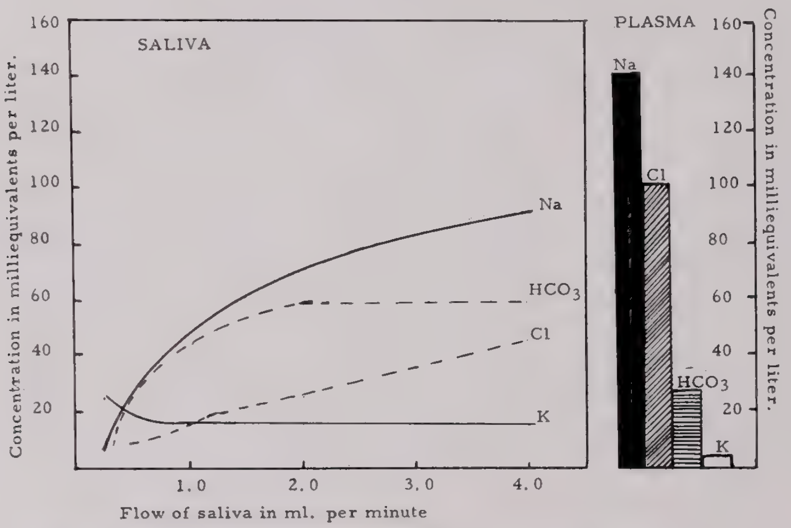
0.1 to 0.3 ml. are used in the renin bioassay.

*From Warzinski and Demerjian: Canad Med Ass J 90:225, 1965.

Continued

who had bilateral adrenalectomy for their disease, the incidence of adrenal cortical adenomas was 21 per cent.[4]

Reviewing Brown's renin assays in hypertensive subjects, Conn points out that in a group of 48 patients, 21 per cent had low renin levels. In another group of 13 hypertensives with low potassium levels, seven had definitely low renin levels and six had low normal levels, which Conn says could have been diagnostic if collected under the proper conditions.[4]



Saliva Na/K ratios	
Normal 0.61 to 3.37. Mean 1.47	Under 0.25 is diagnostic of aldosteronism. Under 1.0 is suspicious of aldosteronism. Thorn, G.: New Engl J Med 267: 1136, 1962.

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*From Thorn et al.: Amer J Physiol 178:156, 1954.

Fig. 2 — Normal Composition of Parotid Saliva.

Diagnostic Criteria

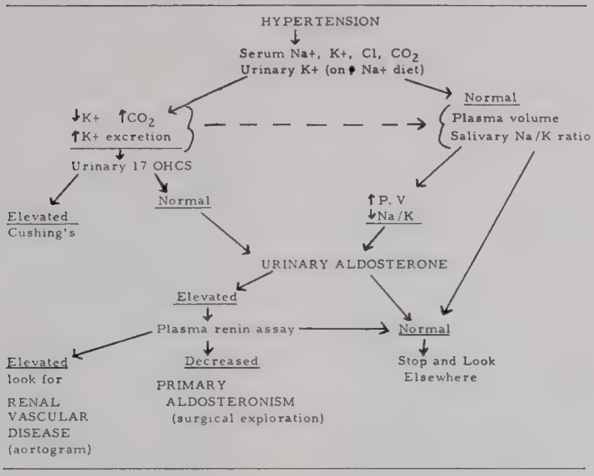
To simply suggest that all hypertensives should be screened with a renin assay is, at this time, totally impractical. While collection and preparation of the sample is no problem (Table 2), the actual assay is much more difficult.[25] The response of a nephrectomized, standardized rat to the infusion of the preparation shows how measurement of plasma renin levels are obtained.[2,25] A simpler method may be available in the future.

Table 3 summarizes a suggested approach to the patient who has hypertension of undetermined cause. Certainly the patient with hypokalemic alkalosis (even if he develops this while on thiazide diuretics) is a prime suspect. Although plasma volume determination has been suggested as a screening procedure, the determination of salivary sodium and potassium content seems to show more promise.[26,27] Figure 2 gives normal values for salivary electrolytes.

It is therefore suggested that while on a diet of 200 to 300 milliequiva-

TABLE 3

Steps in the Diagnosis of Primary Aldosteronism


HYPERTENSION
Serum Na+, K+, Cl, CO2
Urinary K+ (on ↑ Na+ diet)
Normal
Plasma volume
Salivary Na/K ratio
↓K+ ↑CO2
↑K+ excretion
Urinary 17 OHCS
Elevated
Cushing's
Normal
↑P. V
↓Na/K
URINARY ALDOSTERONE
Elevated
Plasma renin assay
Normal
Elevated
look for
RENAL VASCULAR DISEASE
(aortogram)
Decreased
PRIMARY ALDOSTERONISM
(surgical exploration)
Stop and Look Elsewhere

lents of sodium daily, the subject rinse his mouth with 0.5 M citric acid to produce maximum salivary flow. On an adequate volume of saliva, the determination of Na. and K. can be made, and the Na./K. ratio determined. If it is below 1, a 24-hour urine collection is made for aldosterone determination. The subject is then placed on a diet of 10 milliequivalents of sodium daily for at least four days; then, following his being in the upright position for at least four hours, a blood sample is drawn and prepared for renin assay.

The diagnosis of primary aldosteronism can be made if the renin level is low and the aldosterone level is elevated. In the event that both renin and aldosterone levels are elevated, a search for renal causes of hypertension is in order. Table 1 summarizes the clinical conditions in which various combinations of these two substances are present.

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17-27 May be secured from Grand Rounds Editor.

Quite often when a man thinks his mind is getting broader it is only his conscience stretching. — Marathon (Wisconsin) Times

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Who, then, is the invincible man? He whom nothing that is outside the sphere of his moral purpose can dismay. — Epictetus

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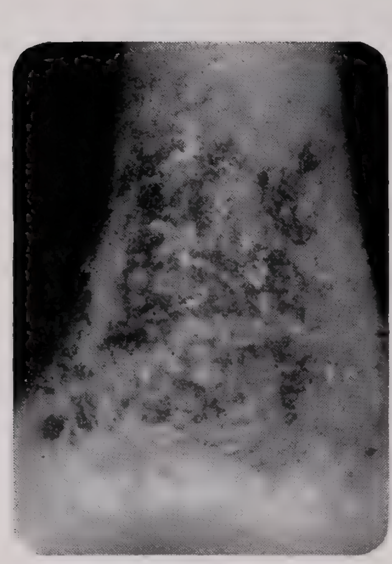
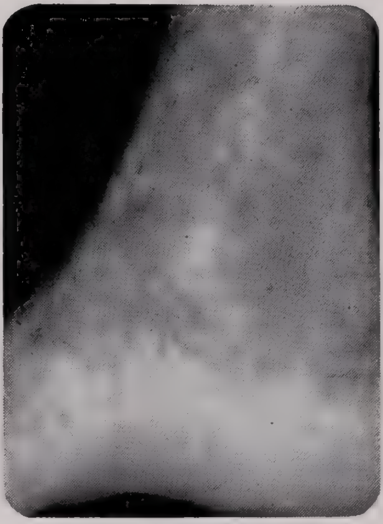


Before treatment



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Book Reviews

Man builds no structure which outlives a book. — E. F. Ware

RADIOLOGIC DIAGNOSIS IN INFANTS AND CHILDREN — Armond E. Brodeur: C. V. Mosby Co., St. Louis, 1965; 503 pages, Price $26.50.

This is a well-illustrated, concise book on pediatric radiology, based on the considerable personal experience of the author.

After an opening chapter, entitled "The Technique of Differential Diagnosis," the book is divided into five sections: Head and Neck, Thorax, Abdomen, Skeleton and Integument, and The Mistreated Child. Each of the first four sections consists of two to seven chapters under headings of the various organ systems. Each chapter or its subdivision begins with a description of the normal anatomy. The congenital and acquired abnormalities are then discussed. Finally, the pitfalls in diagnosis are pointed out. The author's presentation is pertinent and lucid. Of special value is the material on the mandible and the teeth, contributed by Richard J. Parmley.

The references, comprehensive and up to date, appear at the end of the volume. One might wish that they were listed under subject headings rather than authors.

The accomplished pediatric radiologist will find Dr. Brodeur's approach lacking in depth, if not in sophistication. The general radiologist and the pediatrician may discover sins of omission or dogmatism, but will pick up some pearls along the way. For the junior resident in radiology or pediatrics the book will provide a working knowledge and a quick survey of the field before he delves into a larger, standard work. It is primarily for this group and also for pathologists, interns, and medical students that this book is intended. To them it may be recommended.

S. H. Tsai, M.D.
Minneapolis, Minnesota

CARDIAC EVALUATION IN NORMAL INFANTS — R. F. Ziegler, C. V. Mosby Co., St. Louis, 1965.

This small book is concerned with the problems of evaluating the cardiovascular system in the neonatal period. The transition of the circulatory system from the fetal to the adult type pattern must be considered in this evaluation, since it can result in clinical and laboratory findings which may be normal in this age period, but are distinctly abnormal later in life.

The first three chapters are concerned with the definition of normal, the fetal circulation, and changes in the circulation occurring at birth. On this base, the next four chapters are formulated. These deal with evaluation of cyanosis, cardiac murmurs, cardiac rate and rhythm, and the heart size, all of which are problems on which the pediatrician is frequently consulted. In the discussion of these signs or symptoms the various factors causing them and ways to approach them in evaluation are presented. The final two chapters are concerned with more specific problems such as the heart in respiratory distress syndrome and evaluation of growth retardation.

The author's major interest within the field of pediatric cardiology is electrocardiography, and this laboratory tool is emphasized throughout the book and its applications to clinical problems is stressed.

The bibliography is comprehensive. Two deficiencies are noted in the book. The first is that reproduction of the electrocardiogram is poor. The second is that in portions of the book the reading is difficult because of sentence construction. Despite these drawbacks, this book should be useful to pediatricians and to pediatric cardiologists.

James H. Moller, M.D.
Minneapolis, Minnesota

SURGERY OF THE FOOT — Second Edition, Henri L. DuVries, C. V. Mosby Company, 1965, $17.50.

This is an excellent book for all general practitioners who must cope with the multitude of foot problems occurring in everyday practice. Common and troublesome lesions like warts and calluses are not ignored but treated with a thoroughness that reflects the author's extensive personal experience. It is nicely illustrated.

It should be valuable reading for the general surgeon and orthopedic surgeon also. The senior author has, for instance, treated on a referral basis over 150 patients who had had a Keller type hallux valgus procedure that failed to provide a satisfactory result. His words of caution are worthy of attention.

The book is quite detailed and a good reference for office use.

Harrison H. Farley, M.D.
Minneapolis, Minnesota

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References: (1) Based on 23 clinical papers, 1512 cases. Bibliography on request. (2) Bush, I. M., Orkin, L. A., and Winter, J. W., in Sylvester, J. C.: Antimicrobial Agents and Chemotherapy—1964, Ann Arbor, American Society for Microbiology, 1965, p. 722.

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Winthrop Laboratories, New York, N. Y. 10016

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*As many as 9 out of 10 urinary tract infections are now caused by gram-negative organisms: E. coli, Klebsiella, Aerobacter, Proteus, Paracolon or Pseudomonas[2]... However, infections of the urethra and prostate caused by non-gonococcal gram-negative organisms are believed to be less prevalent.

Advances

Antibacterial Management of Infections Due to Gram-Negative Bacilli

Part IV. Principles of Management, Empiric Therapy, and Some Infections of the Respiratory Tract*

WILLIAM J. MARTIN, M.D.**
Rochester, Minneota

HAVING COMPLETED the presentation of the antibacterial agents pertinent to the management of infections due to gram-negative bacilli, we are now in an improved position to discuss some of the various diseases caused by these bacteria and to indicate more specifically which drugs are employed. However, prior to tabulating these diseases, it may be wise to present certain principles of management, as well as the generalities of empiric therapy; this therapy often is required in life-threatening infections when the clinical status of the patient makes initiation of treatment necessary prior to the report of microbiologic data. Such empiric therapy is necessary, for example, when a gram-stained specimen of spinal fluid, especially that from a child, reveals the presence of gram-negative bacilli. Also, therapy may be mandatory when cultures are described as growing a pathogen, yet in-vitro bacterial susceptibility tests may not be reportable for another one or two days. In addition, it is not rare in patients in whom bacteremia due to gram-negative bacilli is strongly suspected clinically, for therapy to be initiated empirically after blood is drawn for cultures. Therefore initial therapy cannot routinely be based on the results of cultures and in-vitro susceptibility tests and consequently is often empiric.

Principles of Management

The principles of management of patients having serious infection due to gram-negative bacilli can be summarized as follows: (1) procurement of samples for adequate microbiologic study and initiation of empiric treatment thereafter if the condition of the patient warrants; (2) reevaluation if results of cultures and in-vitro bacterial susceptibilities later indicate a poor choice of antibacterial therapy, but continuation of the empiric regimen if the patient is doing well; (3) procurement of serum bactericidal tests in selected infections to help determine if the bacteria are eradicable by the regimen employed; (4) administration of the drug or drugs in adequate dosage for a sufficient time; and (5) correction of any condition predisposing to the infection or complicating it.

Empiric Therapy

For the most part, in-vitro susceptibility of the organisms to various antibiotics has only retrospective value in the management of serious infection due to gram-negative bacilli because, as aforementioned, therapy often is initiated empirically before such findings are available and ordinarily is not changed if the patient is doing well. To postpone therapy until the results of in-vitro sus-

Continued

The six parts of this paper were presented, in part, at the Symposium on Antibacterial Agents sponsored by the Southern California Society of Hospital Pharmacists, Los Angeles, California, May 2, 1965.

*See Part III, Minnesota Med 49:1161, 1966.

**Mayo Clinic and Mayo Foundation: Section of Medicine.

ceptibility tests are available would mean a delay of 24 to 48 hours and an increased chance of mortality.

There is no dispute regarding the generalization that best results are obtained when the infecting organisms are sensitive on in-vitro tests to the antimicrobial agents employed; the difficulty lies in the unavailability of such data when the clinical status of the patient makes initiation of therapy necessary.

Recently, combined antibiotic therapy with a tetracycline and streptomycin or chloramphenicol and kanamycin has been the regimen employed most frequently by members of our group in the empiric management of serious infection due to gram-negative bacilli. Such a regimen, begun before results of in-vitro susceptibility tests were reported, in cases in which gram-negative bacillary infection was present or likely, provided broader antibacterial coverage than a single agent. Also, infection due to *Klebsiella-Aerobacter* and *Proteus* organisms appears to exemplify a therapeutic paradox since in some of our cases, in-vitro studies indicated resistance to the tetracyclines and streptomycin; yet combined treatment with these antibiotics was followed by recovery. The exact basis for this remains obscure. The phenomenon does not appear equally applicable to certain other infections such as those due to *Escherichia coli.*

Of our patients with serious infection due to gram-negative bacilli, in whom such empiric therapy has been employed during the last few years, approximately 70% have received both streptomycin and a tetracycline drug, and most of the remaining patients have received chloramphenicol and kanamycin. As empiric therapy, my colleagues and I have preferred tetracycline to chloramphenicol because the latter may depress the marrow, and we have preferred streptomycin to kanamycin, since kanamycin is more likely to cause deafness.

With the advent of newer drugs, we have reevaluated this policy. Colistin, like polymyxin B, has the disadvantage that *Proteus* organisms are usually resistant. Kanamycin, if used alone, has the therapeutic inadequacy of not being effective against many *Pseudomonas* organisms and most *Bacteroides* organisms.

Ampicillin is inactive against *Proteus* organisms that are indole-positive as well as *Klebsiella-Aerobacter* and *Pseudomonas* organisms. Cephalothin is not active against all *Klebsiella-Aerobacter* organisms and indole-positive *Proteus* organisms and usually is inactive against *Pseudomonas* and *Bacteroides* organisms. To date, there is no single agent available that assures complete "coverage" against gram-negative bacillary infections.

A regimen more acceptable than a tetracycline and streptomycin combination would be welcome because of the latter's disadvantages, which include the dual depressive effect on the gram-negative elements of the flora and the increased likelihood of coccal superinfection and of streptomycin's ototoxicity. However, there are also disadvantages with alternative antibacterial regimens. As aforementioned, kanamycin is ototoxic and chloramphenicol is hematotoxic; and when they are used conjointly there is also a dual depressive effect on the gram-negative flora. Polymyxin B and colistin can be neurotoxic, perhaps nephrotoxic, and can induce coccal superinfection. Ampicillin can cause anaphylaxis and the other untoward reactions characteristic of the penicillins and induces superinfection in about 5% of patients. Cephalothin has caused transient neutropenia, perhaps is nephrotoxic, and may induce superinfection from *Pseudomonas* and *Bacteroides* organisms. When the patient's clinical course is satisfactory, usually the empiric regimen is continued despite in-vitro susceptibility tests indicating bacterial resistance.

When the patient is not doing well clinically, the empiric regimen is replaced with the following agents in keeping with the results of the susceptibility tests. Ampicillin, cephalothin, kanamycin, polymyxin B, or colistin may be useful in infections due to *E. coli*; except for ampicillin, the same drugs are considered against *Klebsiella-Aerobacter* organisms. Ampicillin and cephalothin are effective against *P. mirabilis*. Cephalothin and kanamycin may be useful against indole-positive *Proteus* organisms. Polymyxin B or colistin are the drugs of choice against *Pseudomonas*. Ampicillin, cephalothin, and kanamycin may be applicable to *Salmonella* infections.

With these principles of management in mind and the consideration of the frequent need that initial therapy be empiric, the antibacterial management of some of the diseases caused by gram-negative bacilli can be discussed.

Some Infections of the Respiratory Tract

Infections of the upper respiratory tract such as acute pharyngitis, otitis media, mastoiditis, and sinusitis may be caused by *Haemophilus influenzae,* especially in children, but beta-hemolytic streptococci, staphylococci, and pneumonococci more commonly are responsible. In cases of influenzal cause, a tetracycline, ampicillin, or a sulfonamide may be used. Erythromycin occasionally is useful. Because of its hematotoxicity, use of chloramphenicol is avoided.

Obstructive Laryngitis

In children acute obstructive laryngitis with epiglottitis is commonly due to *H. influenzae,* and immediate use of tetracycline-streptomycin, ampicillin or chloramphenicol is indicated. Tracheostomy may be necessary.

Vincent's Angina

Vincent's angina, wherein infection due to fusospirochetal organisms results in multiple ulcers covered with a gray, necrotic pseudomembrane involving the tonsils and pharynx, is best treated with penicillin. However, the tetracyclines also are effective and have use in patients allergic to penicillin.

The Thyroid Gland

Considerable confusion with infections of the upper respiratory tract can be caused by infection of the thyroid gland. Bacterial infection of the thyroid is rare but may progress to abscess formation. Thyroid infection is said to be commoner in goitrous and cystic glands, and in association with a persistent thyroglossal duct. However, normal thyroids can be infected as a complication of bacteremia, cellulitis of the neck, or an infection of the upper respiratory tract. Various cocci or tubercle bacilli may be causative; rarely Enterobacteriaceae including *S. typhosa* have been responsible. A semisynthetic antistaphylococcal penicillin given conjointly with a tetracycline or chloramphenicol would provide initial antibacterial coverage; perhaps ampicillin or cephalothin should be considered. Surgical drainage provides a more specific microbiologic diagnosis and helps prevent spread of infection to the mediastinum.[1]

Pneumonia

Pneumonia caused by *H. influenzae* may be primary in a child but usually is secondary to viral disease in an adult. Tetracycline-streptomycin or chloramphenicol has been the regimen used most often in influenzal pneumonia, but ampicillin and cephalothin probably will have future use.

Pneumonia due to *Klebsiella pneumoniae* is more common in alcoholics, diabetics, and patients with cirrhosis; nearly 50% of such patients have bacteremia. *Klebsiella* organisms have an affinity for the upper part of the lungs, and the reaction often is lobar. Tetracycline or chloramphenicol plus streptomycin has been used most often.

Of the pneumonias due to *Pasteurella* organisms, there is the pulmonic form of plague caused by *P. pestis* and requiring streptomycin-tetracycline therapy. In tularemia caused by *P. tularensis,* streptomycin or a tetracycline may suffice, but in infections due to *P. multocida,* penicillin is preferred. In regard to human plague, the World Health Organization noted the occurrence of 1,457 cases with 121 deaths in 1964; corresponding figures for 1963 were 862 cases and 142 deaths. In South Vietnam there were 300 cases in 1964, as against 115 in 1963. Major areas of human plague in the Americas in recent years have included Ecuador, Peru, Brazil, and Bolivia.

In pneumonia from *Salmonella* organisms, a tetracycline, chloramphenicol, kanamycin, ampicillin, or cephalothin is used, depending on the bacterial species.

Continued

Pneumonia due to other Enterobacteriaceae as well as to *Pseudomonas* and *Bacteroides* organisms is a hazard of penicillin and allied therapy because of antibiotic-induced floral changes. Gram-negative bacillary pneumonia, especially that caused by *Pseudomonas* and other "water bacilli," also occurs after use of contaminated inhalational equipment, resuscitation equipment, tracheal catheters, and tracheostomy procedures, which may deposit inocula of these organisms in the pulmonary tree. In pneumonia due to Enterobacteriaceae, tetracycline-streptomycin and chloramphenicolkanamycin have each been successful; ampicillin or cephalothin is considered in resistant cases. In pneumonia due to *Pseudomonas*, polymyxin B or colistin is used. *Bacteroides* pneumonia is treated with a tetracycline.

Empyema

Empyema due to gram-negative bacilli complicates such situations as pneumonia, chest wall trauma, esophageal disease, and surgery or occurs on perforation or extension of subdiaphragmatic infections. Enterobacteriaceae and *Bacteroides* organisms usually are present in the latter processes. Empyema due to type b *H. influenzae* may be of increasing incidence in children. Systemic antibacterial therapy as previously outlined for pneumonia due to these organisms is given, but the regimen may be altered to include drugs effective against enterococci and staphylococci when the lesion results from a subdiaphragmatic infection. In certain cases, intermittent pleural aspiration and instillation of antibiotics may be carried out. The empyema cavity is aspirated as completely as possible, and the antibiotic is injected in 10 to 20 ml. of saline solution before the needle is removed. The fluid is aspirated daily and, if it is viscous, the cavity is irrigated with 100 or 200 ml. of saline solution before the antibiotic is instilled. If the fluid becomes loculated, enzymatic debridement with either crystallin, trypsin or a combination of streptokinase and streptodornase is considered. The enzymes are injected every two to three days for two to three weeks. Definitive therapy of the lesion may necessitate surgical intervention, especially when it reflects subdiaphragmatic infection.

Abscess

Lung abscess is usually due to coccal organisms, but among the potentially causative gram-negative bacilli are the fusospirochetal organisms, with which infection may result in gangrene. Abscess due to these organisms occurs more frequently in the right lung, ostensibly because the right main bronchus is, except for a slight deviation toward the right, a continuation of the trachea which favors aspiration of contaminated secretion from the oral cavity. Penicillin is the antibiotic of choice. Surgery is necessary in more than 50% of cases.

Chronic Bronchitis

In chronic bronchitis or bronchiectasis characterized by repeated episodes of acute infection or pneumonitis, there is difficulty in identifying the responsible pathogen even when smears and cultures are made of material obtained by bronchial aspiration. In addition to various cocci, *H. influenzae, P. multocida,* and fusospirochetal organisms may be isolated. When such gram-negative bacilli are isolated consistently, use of a drug such as ampicillin is considered. Long-term suppressive antimicrobial therapy to prevent exacerbations has not been consistently successful. Surgery remains the only method of cure in bronchiectasis. Hypogammaglobulinemia, especially of the acquired type, may be characterized by repeated pulmonary infections, including those due to *H. influenzae* which may eventuate in chronic bronchitis or bronchiectasis and for which administration of gamma globulin may be helpful.

Cystic Fibrosis

In cystic fibrosis the prognosis may depend largely on the course of the respiratory involvement. Pathogens isolated from the respiratory tract in victims of this syndrome include various cocci and *H. influenzae* and *Pseudomonas* organisms. Frequent microbiologic monitoring of the respiratory tract and use of specific drugs accordingly may be preferable to attempts at antimicrobial prophylaxis.

Pertussis

Despite in-vitro susceptibility of *Bordetella pertussis* to various drugs including the tetracyclines and chloramphenicol, antibiotic treatment of uncomplicated whooping cough has been disappointing. A tetracycline or chloramphenicol may reduce the severity of the disease, but only if given in the first week of the illness. The typical cough usually does not appear within the first week of the onset, so that by the time the diagnosis is made, antibiotics are of little avail. Bronchopneumonia results from secondary infection usually caused by pneumococci, streptococci, and organisms of *H. influenzae.* In complicating bronchopneumonia due to *H. influenzae,* either streptomycin-tetracycline or chloramphenicol may be effective, but ampicillin and cephalothin warrant consideration.

Reference

1. Morrow, G. W., Jr., Olsen, A. M., and Martin, W. J.: Current Practices in General Medicine. 24. Infectious Pneumonia, a Continuing Problem in Diagnosis and Management. Proc Mayo Clin 37:151, 1962.

Minnesota State Board of Medical Examiners

The Minnesota State Board of Medical Examiners and the State Examining Committee for Physical Therapists have announced that persons desiring to take the examination for registration of physical therapists must be graduates of a school of physical therapy approved by the Board for training physical therapists, in addition to the other statutory qualifications. Persons interested in determining their eligibility to take the examination for registration in physical therapy are advised to contact the Board in order to insure that the school they propose to attend is one approved by the Board.

Grand Rounds

In the fall of 1923 Dr. Bela Schick assumed the Directorship of the Pediatric Department at The Mount Sinai Hospital, New York. From the beginning he held his grand rounds and later his conferences on Thursdays. He started promptly at 9:30 A.M. no matter how small the gathering was. One morning during the depression years in the thirties there was an overflow attendance. Schick was delighted and commented, "There must be an epidemic of health."

The following week when the attendance fell off, Schick remarked, "Practice apparently is already better." — I. J. Wolf, M.D.: Aphorisms and Facetiae of Bela Schick.

Public Speaking

A public speaker is a person who will sit up all night writing a speech that will put an audience to sleep the next day. — Herbert Prochnow

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Abstracts, Briefs and Commentaries

POSTEROLATERAL APPROACH
A BACK DOOR TO INFECTED TIBIAL SHAFT FRACTURES

Nonunion of tibial fractures complicated by a discharging fistula over the subcutaneous surface of the bone calls for special therapeutic measures. The present paper reports on a method given little attention and seldom used, but which was employed successfully in four cases. The fractures had been variously treated, including bone grafts through incisions on the anterior surface of the bone, with nonunion still present several months to more than two years later. In two instances the procedure was the only alternative to amputation.

A posterolateral approach to the tibia permits exposure away from the sinus and from infected unhealthy tissue. The implantation of osteogenic material entails the least possible danger of sequestration when purely cancellous bone is introduced behind the interosseous membrane with only external fixation. The principle is to produce a strong bridging of bone plate behind the interosseous membrane, uniting the tibia and fibula both above and below the site of nonunion.
Operative Technique:

The material used is a large amount of chipped bone from the crest and cancellous posterior part of the iliac bone. The incision in the leg is along the posterolateral surface of the fibula. Dissection is posterior to the interosseous membrane separating the muscles, vessels, and nerves well above and below the fracture line. The tissues are separated subperiosteally from the tibia. The dorsal surfaces of the tibia and fibula are chipped with a chisel. The cancellous bone in an unbroken mass is introduced over this denuded area of bone and interosseous membrane. Hemostasis is secured by compression and the wound is closed loosely. A posterior plaster cast is applied.

Case Reports

Case 1.

A male, 28 years old, was admitted two years after an accident, with nonunion and a discharging fistula. Through the posterolateral approach bone grafting was performed. Support was used for four and a half months. The patient returned to work in six months.

Continued

Case 2.

This patient had a similar history and operation for nonunion and fistula of the tibia two years after injury. After plaster immobilization for three and one-half months he returned to work in six months.

Case 3.

This patient with a similar history of seven months duration was operated upon. Union with bridging bone permitted return to work in four months after surgery.

Case 4.

A female, 33 years of age, sustained a complicated, contaminated comminuted tibial fracture. Eighteen months later she had nonunion and an infected sinus. Similar surgery was instituted. Union of the bones was slow, and 12 months passed before weight-bearing was permitted. The precautionary measure of using a cane for two and one-half years was advisable.

Summary

Bone grafting by the posterolateral approach was successful in four patients with nonunion and infection. This approach permits surgery through a sterile field. Two patients in whom amputation had been contemplated were rehabilitated.

Stanley R. Maxeiner, Sr., M.D.
Minneapolis, Minnesota

Dietrichson, Gustav J., and Storen, Gunnar: Gandnes Sykchus, Lillekammer Fylkes-sykehus, Norway. Acta Chir Scand 129:471, 1965.

SYNOVECTOMY FOR RHEUMATOID ARTHRITIS

The author has used synovectomy of the knee on 50 occasions on patients ranging from 11 to 78 years of age. All of these patients suffered disabling pain with or without instability whenever there was swelling of the synovium. Doctor Narmor and his associates did not consider that the usual x-ray changes associated with rheumatoid arthritis were a contraindication for synovectomy, and they thought that early flexion deformities could be corrected if the patient was relieved of the pain which caused the flexion deformity.

In the technique they removed the thickened synovium from all of the joint surface but did not remove the synovium from the suprapatellar bursa. When the meniscus was found to be invaded by the inflammatory process, it too was removed.

The approach to the knee joint was through a medial and a lateral incision. They reported that the majority of patients were restored to function with not less than a 70-degree arc of motion within a week. They consider that the removal of the synovium relieves the patient's pain and prevents or delays the progress of the disease progress, and they believe that early activity after the operation is of importance.

Carl O. Rice, M.D.
Minneapolis, Minnesota

Narmor, Leonard: Surgery of the Rheumatoid Knee. Amer J Surg 111:211, 1966.

MEASLES AND MULTIPLE SCLEROSIS

Although the etiology of measles encephalitis is not clear, its pathological process is characterized by diffuse disseminated demyelinating lesions. Since a demyelinating process is considered characteristic of multiple sclerosis (MS), the authors investigated the measles antibody titers in the serum of over 100 patients with MS. Spinal fluid titers were similarly investigated in 35 MS patients. The examination of the sera of MS patients by neutralization and complement fixation tests revealed slightly higher antibody titers than did those of healthy control subjects. The cerebrospinal fluid of patients with MS showed measurable antibody titers to measles virus in over 75% of cases tested, whereas control subjects showed no evidence of antibodies. These observations on measles antibodies in the serum and spinal fluid of patients with MS do not imply or indicate a direct relationship, but warrant continuing investigation.

Courtesy of References and Reviews
Journal of the American Medical Association

Adams. J., and Imagawa, D.: Proc Soc Exp Biol Med 111:562, 1962.

A COMPARISON OF HALOPERIDOL AND TRIFLUOPERAZINE: A DOUBLE-BLIND, CONTROLLED STUDY ON CHRONIC SCHIZOPHRENIC OUTPATIENTS*

Haloperidol, an investigational butyrophenone, was compared with trifluoperazine, a well-established and effective antipsychotic agent, in a population of chronic schizophrenic outpatients, using a double-blind technique. After a two-week washout period, 26 patients started the study, with 13 taking each drug. Nine patients completed a three-month trial, five of whom were taking haloperidol. Only two haloperidol patients were sufficiently improved to warrant their continued treatment with this medication; but statistical analysis of the Brief Psychiatric Rating Scale total scores and individual subscores for each drug group after the first month of the trial demonstrated a statistically significant superiority for haloperidol on three subscales. There was a relatively higher incidence of extrapyramidal reactions associated with the study drug. The development of weakness, drowsiness, and depression necessitated withdrawing haloperidol from three patients who completed the study. The dosage ratio utilized may have placed the drug at a disadvantage. However, it may be of value in controlling chronic paranoid patients refractory to other major tranquilizers. The size of the sample in this trial prohibits a more definite statement about the effect of haloperidol on any specific symptom.

William T. Luckey, M.D**
Burtrum C. Schiele, M.D.†
Minneapolis, Minnesota

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*This investigation was supported in part by research grant No. MYP-5106, from the National Institute of Mental Health, U. S. Public Health Service.

At the time the study reported in this paper was conducted, Dr. Luckey was a resident psychiatrist at the Veterans Administration Outpatient Clinic.

**Staff Psychiatrist, Veterans Administration Outpatient Clinic, Minneapolis, Minnesota.

†Professor of Psychiatry, University of Minnesota Hospitals.

THE USE OF AIDES IN PHYSICAL MEDICINE

At a meeting on March 17, 1966, the Minnesota Physiatric Society adopted the position with regard to the use of aides in physical medicine and rehabilitation that such persons be employed only in positions where they are under the close, constant, personal supervision of the qualified person whom they are aiding.

Continued

We urge that this principal be recognized and maintained by the medical and hospital community in Minnesota.

G. Keith Stillwell, M.D.
President
Minnesota Physiatric Society

AUTOMATED SCREENING FOR DISEASE

Two years ago physicians and chemists at Duke University Medical Center started a survey to find out if routine automated screening of blood chemistries uncovered enough disease to justify the expense. They compared the data obtained from blood submitted to the routine laboratory to that done automatically by a multichannel analyser. For their automated tests, they chose glucose, urea, sodium, potassium, chloride, carbon dioxide content, calcium, phosphorous, total protein, albumin, and uric acid. For their patients, they used adults admitted to a university, a community, and a veteran's hospital. They performed the tests on 2846 consecutive patients and showed abnormalities in 850 or 30% of them. In 42% of the 850 patients, automated analysis yielded abnormal tests not ordered by the patient's physician. In about one of every 12 patients, the physicians caring for them considered the unexpected data to be medically significant. The cost of automated analysis of 11 tests on each patient was roughly equal to the usual cost of two standard blood chemistries. The authors conclude that a "profile of admission chemical data" is worthwhile. Because of enthusiastic acceptance by physicians, the tests have been done routinely since early 1965 on all adult patients.

Richard L. Reece, M.D.
Minneapolis, Minnesota

Bryan, D. J., Wearne, J. L., Viau, A., Musser, A. W., Schoonmaker, F. W., and Thiers, R. E.: Profile of Admission Chemical Data by Multichannel Automation: An Evaluative Experiment. Clin Chem 12:137, 1966.

COLON POLYPS

Incidence and distribution of adenomatous polyps of the large intestine were determined by examination of the large intestine in 443 consecutive autopsies. All examinations were performed by the author. The results differed from all previous studies, except one. There was striking statistical agreement with this latter study which was carried out in Vienna over 30 years ago. Only in these 2 studies was there a prospective examination of adequate material by a single, experienced prosector. Findings in the 2 studies probably indicate the actual distribution and incidence of adenomatous polyps in an autopsy population. The incidence of polyps is 30% in the 50-60 age group and reaches a level of 50% to 60% in the 60-80 age group. The distribution of polyps in various large bowel segments in the age group 60-80 differs from that of carcinoma and is contributory circumstantial evidence against carcinoma deriving from adenomatous polyps.

Courtesy of References and Reviews
Journal of the American Medical Association

Chapman, I.: Ann Surg 157:223, 1963.

Nature never makes any blunders; when she makes a fool she means it.
— Josh Billings

The Physician's Workshop

A New Instrument for Obtaining Bone Marrow for Biopsy

ALTHOUGH THERE are various tools for obtaining a marrow sample during life, a need exists for a device which allows interchange of different gauge needles and yields an undistorted marrow core when aspiration fails. The instrument shown in Figures 1 to 3* accomplishes these purposes.

The Instrument

The instrument is made up of two units: "the marrow aspiration instrument" (Figures 1 and 2) and the "tissue core instrument" (Figure 3). The marrow aspiration instrument has four parts — the cap, body, support with chock, and shield with a straight and rounded flange. The unit is equipped with three aspiration needles, a 13, 15, and 17 gauge, each three inches long with a matched bevel point stylet (Figure 2).

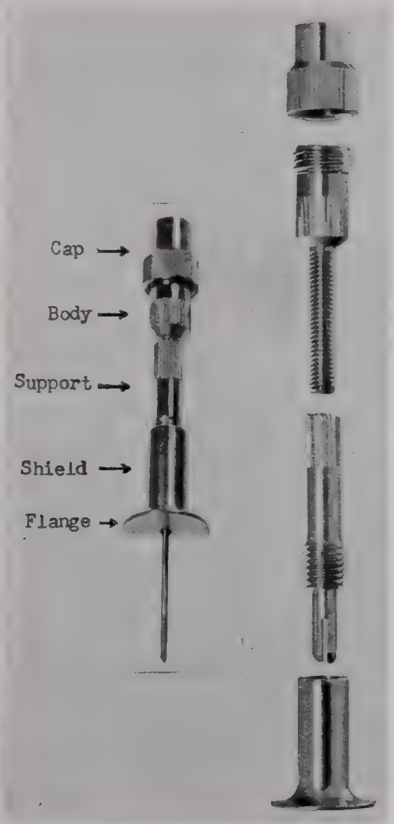

Fig. 1 — Left to right. Assembled marrow aspiration instrument. Disengaged instrument showing its four parts: the cap, body, support with chock, and shield with straight and round flange.

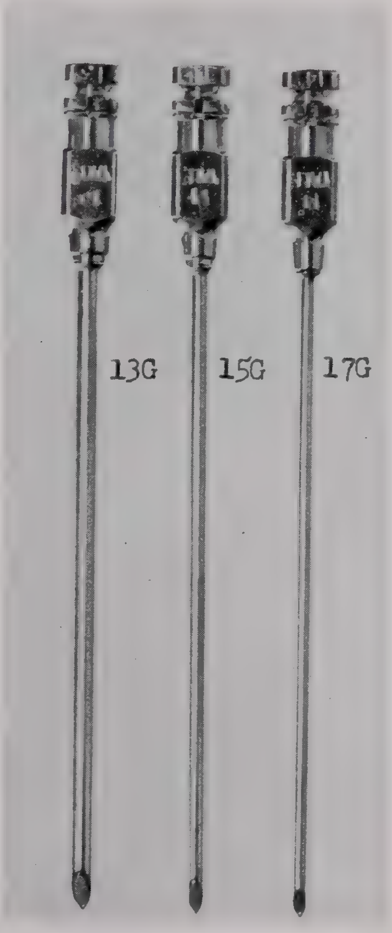

Fig. 2 — Interchangeable aspiration needles 13, 15, and 17-gauge.

Continued

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*Schleicher Marrow Aspiration and Tissue Core Instrument made by Becton, Dickinson and Company, Rutherford, New Jersey 07070.

The Tissue Core Instrument

The tissue core instrument (Figure 3) has three parts, a blunt end stylet, a detachable hub with a set screw, and a 11.5 cm. long disposable core shaft with a razor-sharp bevel. When the core shaft is completely inserted in the hub, the bevel extends 3 mm. beyond the bevel of the aspiration needle. The core shaft, however, can be lenghtened about 1 cm. with the aid of the set screw. The 15, 17 and 19-gauge tissue core instrument shown in Figure 3 fits into the lumens of the 13, 15, and 17-gauge aspiration needles respectively.

The Aspirating Needles

The different gauges of aspiration needles were selected to accommodate the user. A 13-gauge needle is preferred for penetrating the femur, the lumbar vertebrae, and the iliac crest. A 15 and 17-gauge needle is generally used for obtaining a marrow sample from other sites of the skeleton.

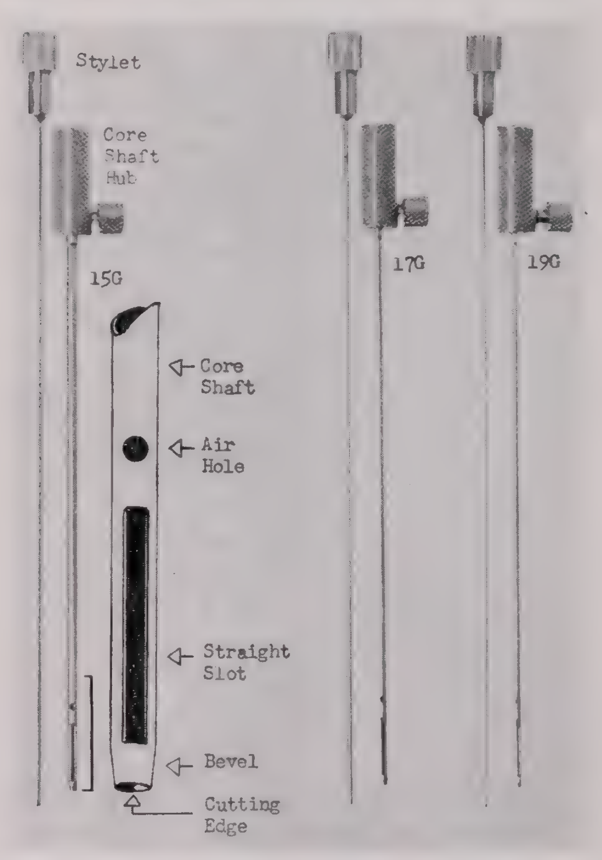

Fig. 3 — Tissue Core Instrument 15, 17, and 19-gauge fitting the lumen of the aspiration needles 13, 15, and 17-gauge in the order given. Drawing shows part of the core shaft, the air hole, straight slot, and the bevel of the tissue core instrument.

Function of the Marrow Aspiration Instrument

The instrument is 7 cm. in length. The design allows a secure grip on the instrument. *The cap* holds the stylet of the aspiration needle firmly in place, preventing dislodgment when the skin and bone are penetrated. The hub of *the body* keeps the aspiration needle hub from turning, and the thread part permits adjustment of the needle length beyond the shield. One complete turn of the body equals 1 mm. The long groove on the body hub serves as a turn indicator. Thus it is possible to accurately adjust the length of the aspiration needle and depth of the bevel in the medullary cavity.

The support together with the shield secures the aspiration needle by turning the support clockwise into the shield. Thus the chock of the support is forced against the conical inner wall of *the shield.* This action results in fastening, stabilizing, and centering the needle in the instrument, a desirable feature because it distributes stress evenly and prevents bending of the needle on hard bone. Though the aspiration needle is tightly secured, the length protruding from the shield can still be adjusted, a feature which is particularly important when the instrument is in situ and bone trabeculae must be broken to obtain a good flow of marrow substance into the syringe. *The flange* of the shield serves as a finger support and minimizes embedding of the shield into the skin. The straight part of the flange allows insertion of the instrument at a 10° to 15° angle, a position used to obtain marrow from ribs, from osteoporotic bones, and from the newborn and the infant. The 15 or 17-gauge needle may be shortened to 2½ inches for exclusive use on the newborn and the infant.

Determining the Length of the Aspiration Needle

The distance the aspiration needle protrudes from the shield is determined before the instrument is inserted into the medullary cavity of the selected bone by passing a small-gauge needle through the skin to the bone surface. The length of the aspiration needle is adjusted by turning the body clockwise or counterclockwise till the length corresponds to the determined distance. The needle length is then further advanced to compensate for the thickness of the anterior lamina of the bone. For example, the anterior lamina of the sternum is 0.8 to 1.5 mm. thick. Thus two complete turns of the body, which equal 2 mm., correct for the lamina thickness. To make sure that the bevel of the aspiration needle will be in the medullary cavity, 1 mm. of length is added (one complete turn of the body). Since the medullary cavity is only 6.0 to 9.0 mm. in depth it is necessary to adjust the length of the needle with care. The straight part of the shield flange should be parallel to the manubriosternal ridge when the instrument is in situ. Turning the aspiration needle several times up and down within the added 1 mm. creates a channel in the trabecular framework that aids in obtaining marrow substance.

Function of the Tissue Core Instrument

The total length of the tissue core instrument is 13 cm. The hollow *core shaft* has a 1 cm. long *straight slot,* an *air hole,* and a razor-sharp *bevel.* The core shaft is secured in the hub with the set screw, which also allows the core shaft to be lengthened about 1 cm.

When a dry tap is experienced the needle of the marrow aspiration instrument is left in situ and the syringe disengaged. The tissue core instrument of corresponding size is then inserted; for example, if a 15-gauge needle is in the instrument the 17-gauge tissue core instrument is used. If a tissue core of more than 3 mm. in length is desired, the core shaft is adjusted accordingly and again secured in the core shaft hub with the aid of the set screw. The core shaft is then passed through the lumen of the aspirative needle. When resistance is felt, the core shaft is gently pressed into the marrow parenchyma while rotating the shaft clockwise. Thus the razor-sharp bevel readily cuts trabeculae, fibrous tissue, marrow, and tumor. That the core shaft may cut through the posterior lamina of a bone is remote, since solid bone tends to dull the cutting edge of the bevel. When increasing resistance is encountered the core shaft is rapidly turned several times and withdrawn.

Irrespective of the kind of specimen obtained, the core shaft is released from the hub and placed immediately in formol-saline fixing fluid* for one hour. The slot and the air hole permit the fixing fluid to come into immediate contact with the marrow sample; thus artefacts are minimized. Since tissue tends to shrink somewhat during fixation the specimen is easily removed from the lumen of the core shaft with the blunt-end stylet. Because the labile tissue core is retained in the cannula until properly fixed, the possibility of damaging the histology

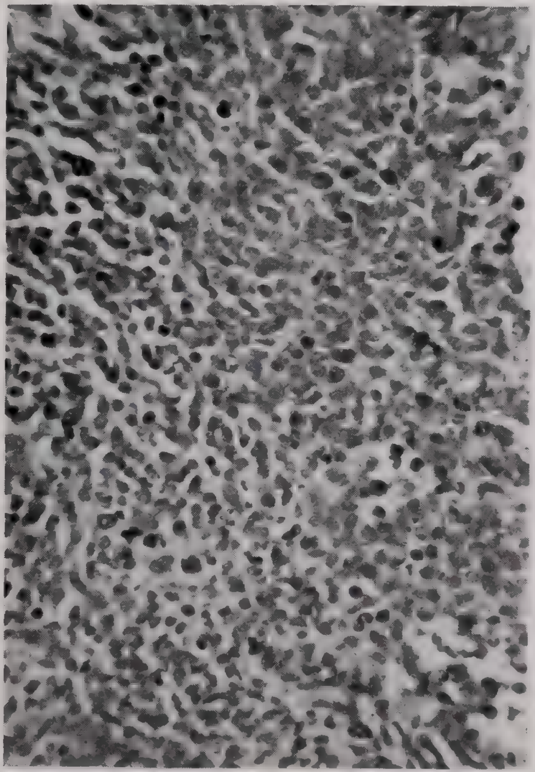

Fig. 4. — Part of a histologic marrow core preparation of a nonaspirable tumor. The specimen was obtained with the 17-gauge tissue core instrument.
Magnification x 500
Hematoxylin-Eosin stain

Continued

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*Neutral Formaldehyde	10 ml.
Physiologic Sodium Chloride Solution	90 ml.

while expelling the specimen is remote. A second unfixed sample may be used for imprint or smear preparations.

Should solid bone in the core shaft bevel prevent the specimen from being expelled, the bone disc is gently pushed into the lumen. If force has to be applied to move the bone disc, the latter is pushed along the lumen expelling the sample from the other end of the core shaft. This procedure does not cause distortion of the histology of a well fixed core. Figure 4 shows part of a histologic preparation of a tumor core obtained with the 17-gauge tissue core instrument.

The tissue core instruments can also be used for obtaining a specimen from other soft organs.

Method of Testing the Sharpness of the Core Shaft Bevel

Razor sharpness of the core shaft bevel is absolutely essential for obtaining an undistorted marrow core. Thus the cutting edge must be tested after each use and before sterilizing the instrument. This can be done in a simple manner. Fold a sheet of Kleenex tissue several times; then rotate and slightly press the shaft against the tissue. A sharp bevel readily cuts into the paper cushion with smooth-edged discs retained in the lumen of the bevel. If no discs are obtained the bevel edge may be sharpened on emery paper No. 000 or honed.

Summary

A new instrument is presented for obtaining a marrow sample for biopsy. The instrument consists of two units: a marrow aspiration instrument and a tissue core instrument. This versatile tool allows procuring of a marrow sample from different sites of the skeleton of all age groups. It provides an undistorted specimen when a so-called dry tap is encountered. The components of both units and their proper use are described.

Acknowledgment

The cooperation of Mr. Edwin A. May, and Mr. Peter R. Halasz, Cardiovascular and Special Instrument Division, Becton, Dickinson and Company, Rutherford, N. J., while working out the basic design of the instrument, is herewith acknowledged.

Emil Maro Schleicher, Ph.D.*
Minneapolis, Minnesota

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*Director Hematology Section, Department of Pathology and Clinical Laboratories, St. Barnabas Hospital.

Amiel's Grievance

The principal grievance which I have against the doctors is that they neglect the real problem, which is to seize the unity of the individual who claims their care. Their methods of investigation are far too elementary; a doctor who does not read you to the bottom is ignorant of essentials. To me the ideal doctor would be a man endowed with profound knowledge of life and of the soul, intuitively divining any suffering or disorder of whatever kind, and restoring peace by his mere presence. Such a doctor is possible, but the greater number of them lack the higher and inner life, they know nothing of the transcendent laboratories of nature; they seem to me superficial, profane, strangers to divine things, destitute of intuition and sympathy. — Henri-Frederic Amiel (1828–1881)

Tribute from a Thinker

But nothing is more estimable than a physician who, having studied nature from his youth, knows the properties of the human body, the diseases which assail it, the remedies which will benefit it, exercises his art with caution, and pays equal attention to the rich and poor. — Voltaire

Special Article

Space Laboratories for Research in Biology and Medicine*

Promising Developments

MAJOR GENERAL OLIVER K. NIESS**
Colorado Springs, Colorado

THE STUDY of life, its origin, preservation, support, texture, composition, chemistry, physics, and evolution has been the occupation of researchers in biology and medicine for centuries past. Life in all its forms has been studied, classified, dissected, and probed for knowledge, understanding and exploitation by man. The biological objects of study have been those adhering to the surface of the earth, immediately above or below, and limited by the physical constraints of that environment.

Man has wrested many of nature's unyielding secrets from living tissue by varying in the laboratory the environmental effects, temperature, radiation, sound, light, and other electromagnetic forms of energy. By changing these energy forms in biological tissue, he has been able to manipulate the living cell, to disrupt its motion, scatter molecules, and force the life form in one fashion or another to reveal its structure.

Manipulating life forms for research with various energy probes is expensive and often difficult because living tissue is easily damaged and changed to nonliving tissue and is tightly bound to the physical constraints of the surface of the earth.

The U.S.S.R., in its space program, has placed a heavy emphasis on biology in space. As related by Parin, "In addition to the dogs, mice and flies were sent into space. Flies are quite sensitive to the effects of radiant energy and a great many could be sent along on the flight."

. . . "As we know, radiant energy, including cosmic rays, is deceptive. Its effects are not felt immediately, but after some time, depending on the intensity of the irradiation to which the organism is subjected.

"The marrow tissue of mice, most sensitive to the effects of radiation, was studied and it was found that there were no harmful

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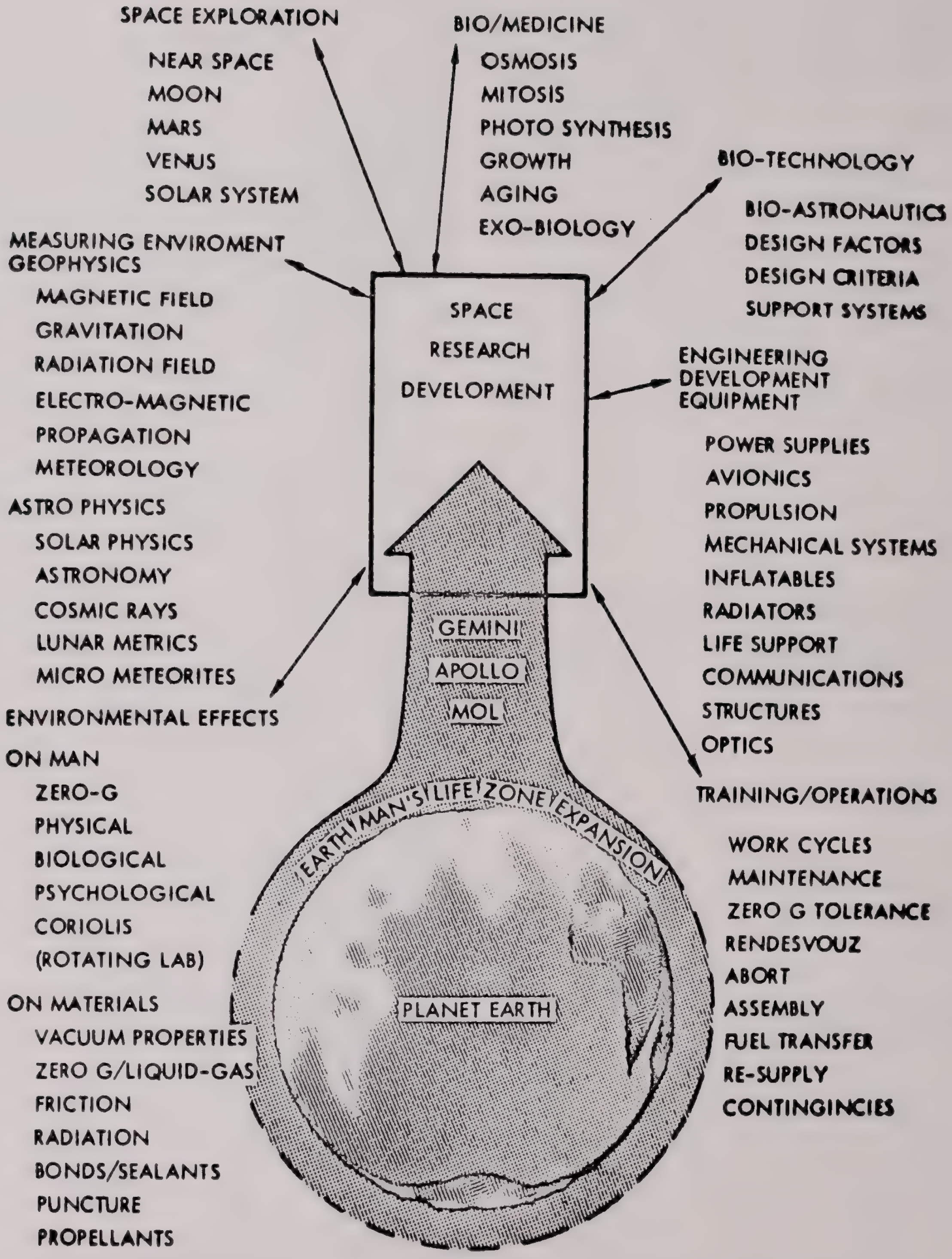
*Presented at the annual meeting of the Minnesota Academy of Medicine, May 12, 1965.

**President of the American College of Chest Physicians, Chicago, Illinois.

Continued



SPACE EXPLORATION
- NEAR SPACE
- MOON
- MARS
- VENUS
- SOLAR SYSTEM

BIO/MEDICINE
- OSMOSIS
- MITOSIS
- PHOTO SYNTHESIS
- GROWTH
- AGING
- EXO-BIOLOGY

BIO-TECHNOLOGY
- BIO-ASTRONAUTICS
- DESIGN FACTORS
- DESIGN CRITERIA
- SUPPORT SYSTEMS

MEASURING ENVIROMENT GEOPHYSICS
- MAGNETIC FIELD
- GRAVITATION
- RADIATION FIELD
- ELECTRO-MAGNETIC
- PROPAGATION
- METEOROLOGY

ASTRO PHYSICS
- SOLAR PHYSICS
- ASTRONOMY
- COSMIC RAYS
- LUNAR METRICS
- MICRO METEORITES

ENGINEERING DEVELOPMENT EQUIPMENT
- POWER SUPPLIES
- AVIONICS
- PROPULSION
- MECHANICAL SYSTEMS
- INFLATABLES
- RADIATORS
- LIFE SUPPORT
- COMMUNICATIONS
- STRUCTURES
- OPTICS

ENVIRONMENTAL EFFECTS

ON MAN
- ZERO-G
- PHYSICAL
- BIOLOGICAL
- PSYCHOLOGICAL
- CORIOLIS
- (ROTATING LAB)

ON MATERIALS
- VACUUM PROPERTIES
- ZERO G/LIQUID-GAS
- FRICTION
- RADIATION
- BONDS/SEALANTS
- PUNCTURE
- PROPELLANTS

TRAINING/OPERATIONS
- WORK CYCLES
- MAINTENANCE
- ZERO G TOLERANCE
- RENDESVOUZ
- ABORT
- ASSEMBLY
- FUEL TRANSFER
- RE-SUPPLY
- CONTINGINCIES

Fig. 1 — Manned Space Exploration Systems Research Development. This very busy slide shows the complex set of systems and technologies which are all involved in manned space flight.

effects on the hemopoietic system. The blood composition also remained normal. Genetic experiments, too, were conducted on the flies."[1]

In addition, the space ships carried plant seeds and shoots. It is interesting that cosmic radiation had a positive effect on the shoots; growth was accelerated.

Manned Orbital Space Station

The manned orbital laboratory task is not to prove that man can orbit the earth in space and survive to return; Mercury and Vostok proved that; but the task is to deploy a laboratory so designed as to make possible basic research on the performance potential of man in space. This mission requires that the exploratory laboratory maximize the research potential and minimize the disadvantages which will prevail in this essentially foreign environment for earth-man scientists. What is called for is an operational space laboratory.

Manned orbital space stations are only a particular mode of space operations, but in the next ten years they will play a dominant role in the development of space research and development laboratories. The space environment has been closely approximated at ground level with three important exceptions: the gravity-free state, the ionizing radiation component, and an infinite unimpeded heat sink.

The Mercury and Gemini projects have provided important data and information for short-term exposures to space. Apollo will provide additional data, but space stations will be the facilities in which the effects of prolonged exposures of months and years can be investigated, and at the same time include provision for the health and performance needs of man.

Biotechnologist

Biotechnological research in manned orbital stations will be designed so that programs: (a) include those which can be effectively executed only in true space or in a weightless state; (b) apply principally to requirements in such areas as design, health, safety, and performance; (c) meet specific needs of national interest; and (d) justify their cost in terms of extent of need for such information and in terms of over-all usefulness.[2]

Many of the experiments will have to do with performance of the manned versus the unmanned system, others with basic areas where man may do better as an investigator and data-acquirer than unmanned probes. Throughout, the laboratory research will be done on earthman himself as a subject in the space environment and, finally, the entire program will be designed to contribute to the follow-on space project.

Essentially, the designer's task will be to:

(1) provide the manned orbital laboratory with an environment which will contribute to and least interfere with research,

(2) provide the manned orbital laboratory with the tools and instruments necessary to conduct required experiments,

(3) provide the manned orbital laboratory with a data system that can manage acquired data, and

(4) provide the manned orbital laboratory with the systems support which will make possible the determination of the potential of manned versus unmanned space systems.

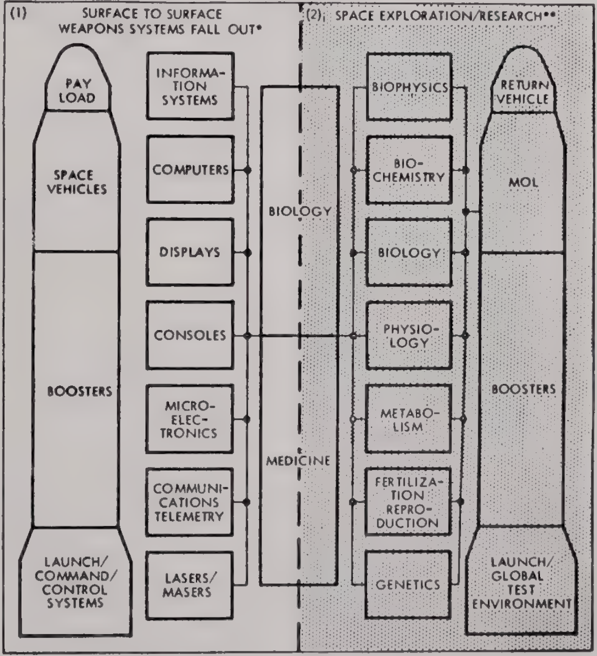

(1) SURFACE TO SURFACE WEAPONS SYSTEMS FALL OUT*
(2) SPACE EXPLORATION/RESEARCH**
PAY LOAD
SPACE VEHICLES
BOOSTERS
LAUNCH/ COMMAND/ CONTROL SYSTEMS
INFORMATION SYSTEMS
COMPUTERS
DISPLAYS
CONSOLES
MICRO-ELECTRONICS
COMMUNICATIONS TELEMETRY
LASERS/ MASERS
BIOLOGY
MEDICINE
BIOPHYSICS
BIO-CHEMISTRY
BIOLOGY
PHYSIOLOGY
METABOLISM
FERTILIZATION REPRODUCTION
GENETICS
RETURN VEHICLE
MOL
BOOSTERS
LAUNCH/ GLOBAL TEST ENVIRONMENT

Fig. 2 — Weapons Systems Fallout — Manned Space Exploration Research. On the left side is a summary of systems now developed which must be applied to support our manned laboratory research program. On the right are some promising areas of study in this laboratory for biomedicine.

Continued

Man vs. Instrument

Comparison of man and instruments for information gathering at the level of raw data puts the human in a highly unfavorable position. In general, instruments are more accurate and more sensitive and can be endowed with much better memories.

Complex Pattern Recognition

Man does have a flair for complex pattern recognition, but this is offset by his gross limitation on processing rate. The most optimistic measurement of human information acceptance rates leads to a figure of around 35 bits per second. Some more stringent tests have suggested rates as low as four or five bits per second. These figures are about six orders of magnitude less than the 5 x 10^7 bits per second rate of a television channel. For elementary processing such as arithmetical operations or simple sorting, computing machines are again faster by factors around a million.

If we are to justify transporting a man into space, we must find a part for him to play beyond sensing or processing. Man has his ability to use language. To compress a vast amount of data into a few symbols is incomparably beyond the capabilities of mechanical coding techniques for communications or programs for computers. In some contexts it is true that a single picture is worth a thousand words. It is also true that in other contexts a single word can sum up a thousand pictures.

Novelty Interpretation

The other characteristic of man that recommends itself is his ability to recognize and interpret novelty, to see significance in small deviations from the ordinary. This quality enabled Volta to notice a frog's leg twitching and surmise that it was a sign of chemical involvement with electricity and caused Fleming to interpret a bit of mold in his bacteria culture as something other than a contaminant. In a more modest fashion the same phenomenon was at work in singling out the "Glenn effect." This ability is no better understood than the powerful coding effect of language. Worse, it is even less controllable. For the one instance where a Fleming sees a new effect, hundreds of technicians have poured the mess down the drain. Putting a man in a spaceship does not guarantee that he will experience serendipity. On the other hand, not putting him there virtually guarantees that the novelties will be missed.[3]

The law of geotropism says that in a plant, when the seed germinates, the roots will grow down and the stem up.

What will it do in Zero-G? Will roots grow all around? As yet we do not know. The molecular behavior of liquid and gas in the cell membrane and all around it will be altered in Zero-G. How this will affect the cell and its basic processes we do not know.

If there are life forms on Mars that are very similar to life forms on Earth, then Gulliver is likely to report them; but if there are life forms whose metabolism is like nothing on earth, we will have to rely on our astronauts.

Space Laboratory

The space program will make available to the researcher in life forms a laboratory of energy around which he can re-examine the entire spectrum of basic assumptions and

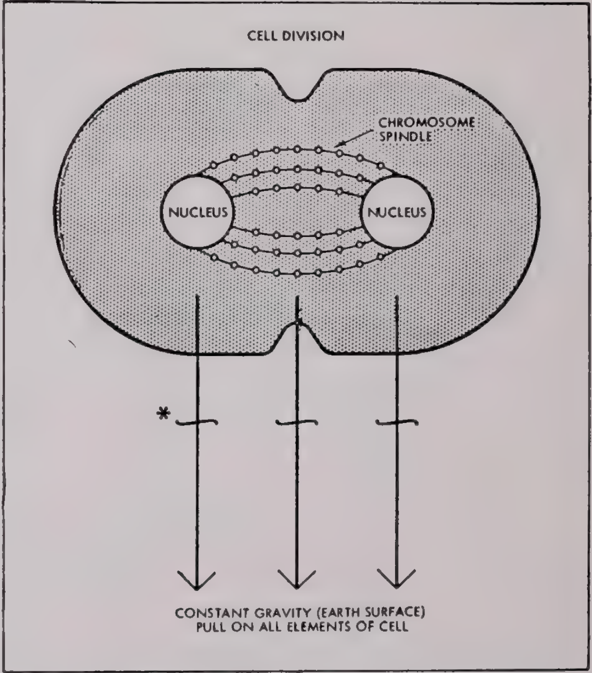

CELL DIVISION
CHROMOSOME SPINDLE
NUCLEUS
NUCLEUS
*
CONSTANT GRAVITY (EARTH SURFACE) PULL ON ALL ELEMENTS OF CELL

Fig. 3 — Mitosis in Zero G. Fig. 3 illustrates the extraordinary problem of cell growth and division in Zero-G. Does the gravity vector and constant pull affect the polarity and distribution of the chromosome spindle? As yet no one knows.

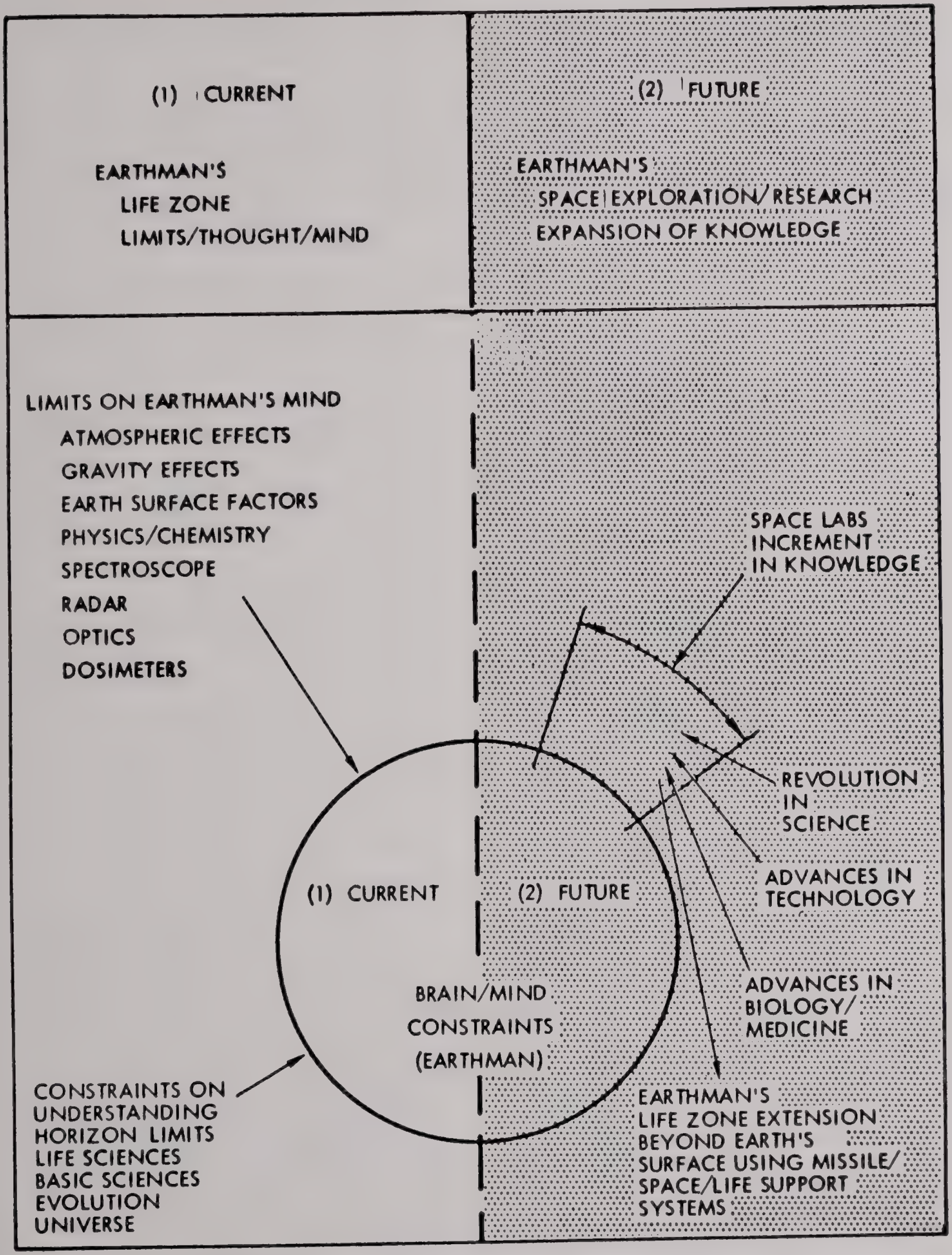

(1) CURRENT
EARTHMAN'S
LIFE ZONE
LIMITS/THOUGHT/MIND
(2) FUTURE
EARTHMAN'S
SPACE EXPLORATION/RESEARCH
EXPANSION OF KNOWLEDGE
LIMITS ON EARTHMAN'S MIND
ATMOSPHERIC EFFECTS
GRAVITY EFFECTS
EARTH SURFACE FACTORS
PHYSICS/CHEMISTRY
SPECTROSCOPE
RADAR
OPTICS
DOSIMETERS
SPACE LABS INCREMENT IN KNOWLEDGE
REVOLUTION IN SCIENCE
ADVANCES IN TECHNOLOGY
(1) CURRENT
(2) FUTURE
ADVANCES IN BIOLOGY/ MEDICINE
BRAIN/MIND CONSTRAINTS (EARTHMAN)
CONSTRAINTS ON UNDERSTANDING
HORIZON LIMITS
LIFE SCIENCES
BASIC SCIENCES
EVOLUTION
UNIVERSE
EARTHMAN'S LIFE ZONE EXTENSION BEYOND EARTH'S SURFACE USING MISSILE/ SPACE/LIFE SUPPORT SYSTEMS

Fig. 4 — Anticipated Expansion of Earthman's Knowledge in Science and Technology from the Manned Space Laboratory Research Program. Fig. 4 illustrates this quantum jump in the capabilities of man's mind which will occur from our space explorations and which will profoundly affect our sciences and technologies and biomedicine. On the left we show the limits, the constraints on man's inquisitive intellect; for, as the Apostle Paul said, "Now we see through a glass darkly, then face to face." And, indeed, the heavens will open to us in the space program.

Continued

facts which man has gleaned from centuries of painstaking study. For the first time he will have at his disposal a laboratory for life forms beyond the surface physics and chemistry of this earth.

This laboratory of such penetrating energy and varying physical constraints can be expected to bring about a leap forward in man's understanding of life and of the basic sciences themselves, which are all avenues for the understanding of life and its structure.

As never before, we are also beginning to grasp the severe limitations of earth-bound "brains" and thought. Historically, the best minds of men have applied their energies vigorously to these problems, and in some perplexing areas results have been almost always negative.

Human beings are two-dimensional creatures tied to a surface of positive curvature by gravity. We live at the interface between a layer of gas and a layer of solid and liquid. It is only in the past half century that we have begun to move away from the interface, upward and downward with minor oscillations. In the next decade radical departures from our billion year environment will be attained.[3]

If one examines the swift changes which have rapidly carried science and technology ahead in the past few years, further than in previous decades or centuries, it is evident that the mind of earthman enlarges its scope to every facet of its known world. When this level is attained, exploited, and understood, a plateau is reached until some vehicle or communications link, or sensor, can bridge the gap between the known and the unknown.

For earthman space is becoming an opportunity for the analysis of terrestrial science against the backdrop of extra-terrestrial forces. The manned space laboratory program will provide the tools, instruments, experiments, scientists, and support systems for conducting this exploration.

The vast accumulation of data from space explorations will be quickly assimilated by man's mind and the next step forward in science and technology will be under way.

The philosopher Kant pointed out that all the things we know for sure are things which the mind imposes on our picture of the world. He was vague on details of how this imposition occurred or what determined the structure. Kant and most philosophers have felt that there was some special necessity about the categories or mental molds into which we poured our knowledge of the world. More recent studies by psychologists and sociologists suggest that these molds are at least partly conditioned by environment. There are fascinating hints by psychobiologists that certain mental frames may be hereditary and represent a form of biological learning that is as subject to natural selection as tooth size or running ability.

I would like to quote a section of the article entitled "Brain" in the Ninth Edition of the Encyclopedia Brittanica by the great brain surgeon, Sir Charles Sherrington. The section is entitled, "Had Man Had Wings," and the entire section is written with the same harsh magniloquence.

"An interface from the course of evolution of the vertebrate brain is that the freeing of a limb-pair for more manifold use as a 'tool' while the other limb-pair, still assured efficient land locomotion, gave an impulsion or opportunity for cerebral development which was of decisive importance in the evolution of pallial growth and function. This inference raises the surmise that, had wings arisen in the vertebrates, as actually in the insect, without cost of a limb-pair to coexist with 'land-locomotor,' the leg, and 'tool,' the arm, the consequent additional experience and exploitation of a great three-dimensional medium (containing, unlike water, ample oxygen), then would have evolved a brain of wider components and on fuller lines than is the human. A sobering reflection is that should such a vertebrate form, fraught with transcendent promise though it were, enter now upon evolution, man's dominance, leaving no part of the planet's surface untouched, would assuredly meet it and frustrate it by extermination, or by domestication. . . . It would look as though after all, the upward development of mind were not (at least on this planet) an object of the scheme of things."

Sherrington was trying to imagine a mind less hampered than his own. It is no wonder his rhetoric is labored and his thoughts tortuous. Nevertheless, his attempt was in itself a partial counter to his own point. Man appears to have been endowed with a brain richer than his limited experience.

Up to now we have learned most of what we know about the universe beyond the lower atmosphere from light signals, plus an extrapolation of what we know from earthbound laboratories. In recent years other segments of the electromagnetic spectrum have been added, and some information has been gleaned from the debris of cosmic rays. It is amazing how much has been inferred. Light is a remarkably rich carrier of information once the code is broken. But we have been like goldfish in a bowl, attempting to reconstruct what goes on in the bigger world from filtered and refracted images.

Much of the complexity of what we perceive, the structure of things, is furnished by eyes and ears. However, the sense of reality is established by the cruder senses: touch and the kinesthetic feelings. Space flight will allow the analog of touching what we have only been able to see, of realizing what we have only been able to infer, and bringing those "maybes" into the world of solid reality. The probabilities are that a transformation of world view will occur at least as dramatically as the Copernican and Darwinian revolutions.[4]

Summary

Beginning with the manned orbital laboratory, space science will assume a new dimension — that of research in human performance potential and in biology and medicine. Earlier spacecraft determined if manned flight was possible and, if so, to prove out systems to make the flight possible.

Space laboratories will provide a unique test and research environment for biology and medicine, due to the drastic changes in force fields of gravity, time, space, and energy constraints under which all things live on the planet's surface. This laboratory will make possible not only entirely new and unpredictable advances in understanding by man, but coupled to all of the other accomplishments of man's brain will be a quantum jump in the evolution of new understanding.

No one can foresee how fast or how far space research will carry biology and medicine. To date, most of the fallout from missile and space programs has been peripheral, that is, applications of systems primarily developed for weapons. Now with the manned orbital laboratory, the object is the discovery of new data on life, on man, and on all of his performance potential, the greater share of which will be in his "brain" in the new dimension of space.

Admittedly, there exists a weapons potential in space, but the results of these laboratory investigations will likely have their most profound effect in helping man to unravel many of the puzzling problems in biology and medicine right here on the surface of the earth.

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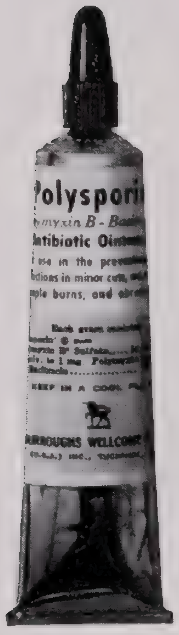

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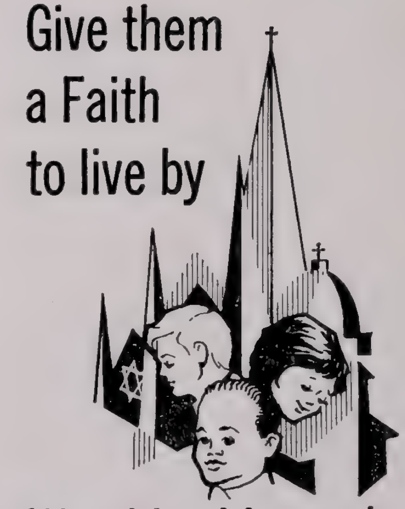

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History of Medicine

Dilatation of the Heart*

P. E. SHEPPARD, M.D.
Hutchinson, Minnesota
Written 1900

WITHOUT THE least claim to originality of research or anything new to present in the line of treatment, I will briefly outline the subject of dilated heart.

I believe it to be a subject of interest to all who practice medicine, and an occasional review is profitable.

A study of cardiac dilatation cannot be separated from that of hypertrophy, for these two usually go hand in hand; but dilatation is a condition well worth consideration by itself and has a chain of symptoms all its own.

Three forms are recognized:

1. Simple dilatation with little or no change in the wall;
2. Hypertrophic or active dilatation (the most common form);
3. Atrophic or passive dilatation.

Morbid Anatomy

The structural changes depend upon the morbid processes which attend the dilatation. From pericarditis and endocarditis there will be serious infiltration and granular degeneration of the muscle fibers. As the result of fatty degeneration the muscles show fatty changes.

The morbid gross anatomy depends largely upon the mechanical condition, and the shape and outline depend upon the part involved. If the dilatation is confined to the right ventricle the heart will increase in breadth; while if confined to the left ventricle the heart will be elongated, with the whole organ affected as in aortic insufficiency.

The endocardium is often opaque. The trabeculae may be reduced to mere fleshy tendons. One or all of the heart cavities may be the seat of dilatation: most commonly the auricles, next the right ventricle, and least frequently the left ventricle (Loomis).

There is always more or less relative insufficiency of the valves from simple separation.

Etiology

Dilatation may take place, first from any cause which may weaken the heart, such as inflammatory conditions or degeneration of the heart itself, or from constitutional states and acute diseases such as pneumonia, typhoid, etc. Such may be termed primary dilatation. Second, all the causes of hypertrophy, when acting on a weak heart, may cause dilatation. They are mostly obstructive in their nature and include valvular stenosis and insufficiency, atheroma and renal disease.

Such dilatations are preceded by hypertrophy and develop as degeneration sets in or may occur acutely on overstrain, fright, etc.

Obstruction

A glance at the mechanism of the heart will serve to show how obstruction and valvular changes can bring about dilatation of the several cavities. Beginning at the left ventricle and going backward we first find heightened systemic blood pressure, which throws the burden of the work upon the left ventricle. To meet this increased demand of

Continued

This paper was written by P. E. Sheppard, M.D., Hutchinson, Minnesota, who was a member of the first graduating class of the University of Minnesota. He started in 1889, was graduated in 1891, and wrote the paper about 1900. This was found among some of my mother's possessions in November 1963. — Charles G. Sheppard, M.D., Le Sueur, Minnesota.

force, hypertrophy occurs, and when the muscle can no longer compensate, dilatation follows.

Aortic Stenosis

Aortic stenosis brings about a similar chain of results. As the left ventricle fails, the increased pressure is backed up into first the left auricle, accompanied by relative insufficiency of the mitral, next, from ensuing pulmonary engorgement into the right ventricle; then the right auricle follows in yielding to the morbid process. Beginning with mitral insufficiency a similar chain of events ensues.

Mitral Stenosis

Beginning with mitral stenosis the picture is altered inasmuch as the left ventricle is left unchanged or even atrophied from insufficient work to do and lack of blood supply. The rest of the heart may then take the usual course of hypertrophy and dilatation.

With pulmonary obstruction the left heart is practically left out of the process; the right only suffers. Thus the disturbances may be traced back to the inflowing blood from the venae cavae.

Symptoms

Pain is not a prominent symptom but may be quite severe and radiate down the arms, especially the left arm. Palpitation is often complained of. A feeling of undefined distress and pressure may be present, and there is a tendency to sighing respiration. Dyspnoea on slight exertion is noted and later becomes very distressing, especially at night, so that the patient is obliged to sleep in a semi-recumbent posture or sit with the head resting on the arms. As the trouble increases the patient's countenance assumes a pale, anxious expression with more or less lividity of the lips. The extremities are cold.

Dyspeptic symptoms are often present and there is more or less mental disturbance. The urine becomes scanty and there is more or less albumin. There will be puffiness of the ankles and later general anasarca. Respiration becomes rapid, 30 to 40 to the minute, and speech becomes difficult from shortness of breath. Paroxysms of dyspnoea are frequent and syncope may be fatal. The patient usually dies from general anasarca or pulmonary edema.

Physical Examination

Physical examination reveals an enlarged and diffused area of cardiac pulsation, and it is difficult to locate the apex beat. Epigastric pulsation occurs in dilatation of the right ventricle. Palpation shows the feebleness of the heart action, an undulating motion, and perhaps a purring thrill. Percussion shows a greatly increased area of dullness which may extend from the right nipple to the left axilla. Dilated auricles may be recognized by an upward increased area of dullness.

The sounds of a dilated heart are weak and indistinct, it being often difficult to distinguish the first from the second sound. Murmurs are confused and uncertain.

The Diagnosis

Thus the diagnosis of dilated heart rests upon feeble heart action, undulating pulse, indistinctness of apex beat, lateral increase of percussion dullness, short, abrupt, and feeble heart sounds that strikingly resemble each other, a feeble, irregular, intermitting pulse, accompanied by the general symptoms of pulmonary and systemic obstruction and congestion.

Prognosis

Prognosis depends upon the removability of the cause, the age of the patient, etc., but should always be looked upon as grave.

Treatment

Treatment resolves itself into the treatment of the primary cause and attention to the symptoms. For the dilatation itself rest of body and mind are essential and attention to general body nutrition is important. A few days or weeks in bed will in many cases give great relief. An exclusive milk diet will often do much good and stimulants should be avoided. The patient should be warned against sudden physical exertion. Flannel should be worn next to the skin.

Besides digitalis, iron and strychnine are the most useful drugs. The cold bath seems to have a decidedly beneficial action, probably from its tonic effect. Venesection will relieve extreme engorgement and often save life.

I wish to report a few cases that have come under my observation during the past few months.

Case Reports

Case 1

H. L., female, 14, has had several attacks of chorea since five years of age. In March 1898 the attack was accompanied by a well marked case of inflammatory rheumatism and endocarditis. In April 1899 the rheumatic symptoms were slight but endocarditis well marked, and dilatation of the heart took place. In the course of a few weeks compensation was restored and the child was able to attend school. In March 1900 dilatation reappeared with all the classical symptoms and was extreme.

With rest in bed, digitalis, cold baths, etc. compensation is partly restored and the patient is about and comfortable.

The meaning of "endocarditis well marked" is for the reader to determine. The modern physician would have included an auscultatory description of the heart and a plethora of laboratory studies, but he could not improve upon the result: "about and comfortable." Editor: R. B.

Case 2

E. S., male, 63, came under my observation in February 1900. He was a subject of chronic Bright's disease. Heart action irregular but fairly good. Chegas Stokes respiration. Hypertrophy of heart well marked.

General anasarca was extreme. This was completely reduced by elaterium* and wet packs and the patient was in a condition of comparative comfort up to April 18 when he died from acute dilatation in about one hour from beginning of attack.

Blood pressures were not routinely measured in 1900. The patient was probably fibrillating, and digitalis might have proved life-saving. The editor has had no experience with elaterium. Editor: R. B.*

Case 3

L. D., male, 56, apparently in perfect health up to last February when he had an attack with weakness, constipation, dyspnoea, and an extremely slow pulse, 40 to 45. No pain. Recovery was not complete. I saw him first on July 6, 1900. Found respiration 38 to 40, pulse about 70, weak, irregular, and intermittent. Rales and dullness over lower and middle lobes of right and lower of left lung. Urine contained considerable albumin. No casts could be found.

Right heart dilated and a relative regurgitant-tricuspid murmur. Apex in 6 intercostal one inch to left of nipple. Some mental disturbance.

Patient was taken to Dr. J. W. Bell of Minneapolis who found fluid in the right pleural cavity. No history of pleurisy, no pain at any time. Symptoms now improving under rest and digitalis.

He might have been a candidate for a pacemaker. Editor: R. B.

I select these three cases because of the variety of etiology to result in the same lesion.

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*See Test Your Word Score Page 1267.

Sceptical France

Even if doctors apply all their knowledge, and act in good faith they often do harm when they think to do good and do not perceive their mistake until the patient has passed beyond . . .

The ignorance of many so-called doctors we know to be so great that it would provide subject matter for a large volume . . .

I should add a word about . . . surgeons; nothing new certainly, for every day we hear many accusations against them; that they carry on to twenty or thirty dressings what could be finished at the third or fourth: that they prolong wounds and sometimes stir them up instead of healing them; and that their wretched ignorance often makes it necessary to amputate an arm or leg. — Estienne Henri (1528–1598)

Life is compatible with any disease, provided the bowels remain open; any kind of pain, provided the heart remains unaffected; any kind of uneasiness, provided the head is not attacked; all manner of evils, except it be a bad woman.

— The Talmud

One third of the people in the United States promote, while the other two thirds provide. — Will Rogers

"The Measurement of Depression"

"THE MEASUREMENT OF DEPRESSION" is a film* depicting the development, validation, and use of a scale for the quantitative measurement of depression.

The scale was designed by Dr. William W. K. Zung[1] Durham, N. C., psychiatrist. Although initially devised for use in psychiatric research, it readily lends itself to the general practice of medicine where most depressions are first encountered.

The film is designed for medical educational purposes at meetings of hospital staffs, county societies or specialty groups. The self-rating scales, available in quantity for use in office practice, come complete with full instructions. Both the film and pads of the self-rating scale are available free upon request from Lakeside Laboratories, Inc., Milwaukee, Wisconsin, 53201.

The scale consists of a list of 20 statements expressed in the common language of the patient. The statements comprehensively delineate widely recognized symptoms of depression including disturbances of mood, biological and psychological function. Testing and scoring patients usually requires less than five minutes. Use of the scale in a variety of patients with physical complaints without apparent organic basis may uncover and measure depression in so-called "hidden depressions" saving valuable time in the clinic and several sessions of probing interviews.

In patients in whom depression is suspected, but is obscured by anxiety or by normal grief, the scale can be used to provide a quantitative index of depression which may be compared with depression ratings obtained in hospitalized and office patients with a variety of emotional disturbances.[1,2]

Depression is a condition of paradox and contradiction. It is sometimes a self-limiting disease with a duration of six to eighteen months, but it may persist for years. It may be obvious or be hidden — from the patient and from the physician.

The depressed patient's grasp of reality usually appears to be undistorted. Even so, suicide makes it necessary to classify depression as a potentially fatal disease. Depression is today's most common and most challenging diagnostic problem, in psychiatry as well as in the general practice of medicine.[4] Despite its high incidence and much that is known about it — the diagnosis of depression often requires from months to years.[3]

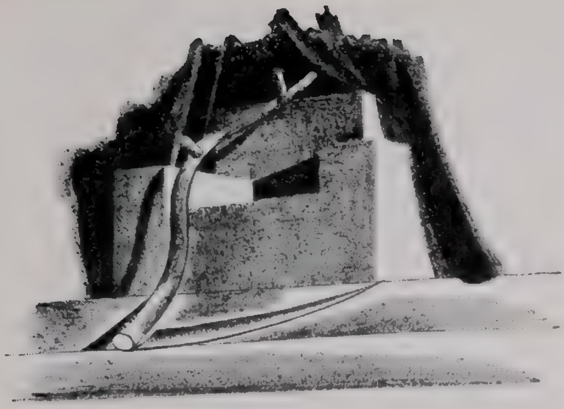
---

*Running Time: 22 minutes. 16 mm., sound and color. Produced by: Sturgis-Grant Productions, Inc. Sponsored by: Lakeside Laboratories, Inc. The film is available on loan without charge. To schedule a showing of THE MEASUREMENT OF DEPRESSION, please see your Lakeside Professional Service Representative or write or phone Medical Film Department, Lakeside Laboratories, Inc., 1707 East North Avenue, Milwaukee, Wisconsin 53201.

References

1. Zung, William W. K.: A Self-Rating Depression Scale. Arch Gen Psychiat 12:63, 1965.
2. Zung, William W. K., Richards, Carolyn B., Short, Marvin J.: Self-Rating Depression Scale in an Outpatient Clinic. Arch Gen Psychiat 13:508, 1965.
3. Stone, T. T., and Burris, B. C.: Melancholia: Clinical Study of 50 Selected Cases. JAMA 142:165, 1950.
4. Dunlop, Edwin: The Treatment of Depression in Private Practice. Dis Nerv Syst XXII: 5:46, 1961.

I could prove God statistically. Take the human body alone — the chances that all the functions of the individual would just happen is a statistical monstrosity.
— George Gallup



In Memoriam

One may live as a conqueror, a king, or a magistrate; but he must die like a man.
— Daniel Webster.

CHARLES ROGER SULLIVAN, M.D.

Dr. C. Roger Sullivan, 44, a member of the Section of Orthopedic Surgery of the Mayo Clinic from 1955-1966, died July 3, at Augusta, Georgia, of the attendant effects of pneumonia. He was a member of the faculty of the Medical College of Georgia.

Dr. Sullivan was born in Cincinnati, Ohio, and received his degree of doctor of medicine from the University of Rochester School of Medicine and Dentistry. He came to Rochester, Minnesota, in January, 1951, as a fellow in orthopedic surgery of the Mayo Graduate School of Medicine. In 1954, he was appointed an assistant to the staff of the Mayo Clinic, and in 1955 he was appointed to the staff of the Mayo Clinic. Dr. Sullivan was certified as a specialist in orthopedic surgery in 1956 by the American Board of Orthopaedic Surgery.

In 1966, he left the Mayo Clinic to become a member of the faculty of the Medical College of Georgia at Augusta. Dr. Sullivan was a fellow of the American College of Surgeons, a member of the Zumbro Valley Medical Society, the Southern Minnesota Medical Association, the Minnesota State Medical Association, the Minnesota-Dakota-Manitoba Orthopedic Society, the American Medical Association, Orthopedic Research Society and the Alumni Association of the Mayo Graduate School of Medicine.

Dr. Sullivan is survived by his wife and six sons.

MYRON W. SMITH, M.D.

Dr. Myron W. Smith, 94, physician and civic leader in Red Wing for more than half a century, died June 14, at the Colonial Acres Nursing Home in Golden Valley. He was born in Rockford, Illinois, and received his medical degree from the Boston University School of Medicine.

Dr. Smith was president of the first Goodhue County Sanatorium, a past president of the Goodhue County Medical Society, Goodhue County Soldiers Memorial Association and the Goodhue County Historical Association. He was a life and 50 Club member of the Minnesota State Medical Association and a member of the American Medical Association.

He is survived by his three daughters.

CLAIR C. CRAIG, M.D.

Dr. Clair C. Craig, 89, International Falls physician, died May 15. He was born near Elk River, Minnesota, and received his degree in medicine from the University of Indiana. In 1917 he went to International Falls to become associated with Dr. Mary Ghostley. In 1920 he opened up his own private offices.

He was a member of the Upper Mississippi Medical Society and American Medical Association and a life member of the Minnesota State Medical Association. Dr. Craig was also a member of many civic organizations in International Falls.

He is survived by his son and two daughters.

ARMER H. STOLPESTAD, M.D.

Dr. Armer H. Stolpestad, 57, St. Paul physician, died May 31st. Born at Lafayette, Minnesota, Dr. Stolpestad practiced on the East Side of St. Paul for thirty-one years. He received his medical degree from the University of Minnesota medical school, and interned at St. Mary's hospital in Duluth.

He was a member of the Ramsey County Medical Society, Minnesota State Medical Association and the American Medical Association.

He is survived by two daughters and two sons.

SIDNEY C. BLACKMORE, M.D.

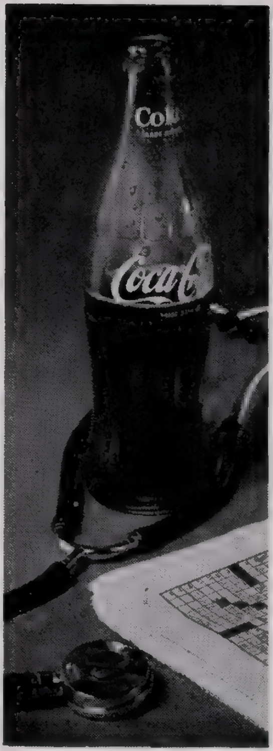
Dr. Sidney C. Blackmore, 53, medical doctor at the Erie Mining Company in Biwabik, died July 3. Born in Rainy River, Ontario, Canada, he lived in Duluth for some time and graduated from the University of Minnesota Medical School. He moved to Biwabik in 1946 and in 1954 joined the East Range Clinic in Aurora.

He was a member of the Range Medical Society, American Medical Association, Minnesota State Medical Association and was a past commander of the Knights Templar Lodge of Eveleth.

He is survived by his wife and three sons.

Coke
Coca-Cola

11:47 pm



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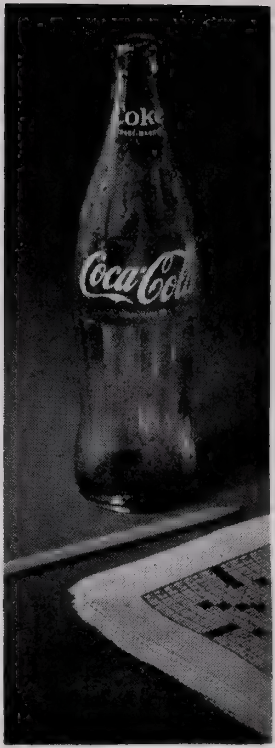

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Meetings and Announcements

When a nation gives birth to a man who is able to produce a great thought, another is born who is able to understand it and admire it. — Jouvert

AUGUST

American Academy of Physical Medicine and Rehabilitation, Sheraton Palace Hotel, San Francisco, Aug. 28-Sept. 2. Sec.: Harriet E. Gillette, M.D., Cleveland Clinic, Cleveland.

American Association of Electromyography and Electrodiagnosis, Sheraton Palace Hotel, San Francisco, Aug. 28. Dir.: Max Karl Newman, M.D., 16861 Wyoming Ave., Detroit 48221.

American Congress of Physical Medicine and Rehabilitation, [E, M], Sheraton-Palace Hotel, San Francisco, Aug. 28-Sept. 2. Exec. Dir.: Creston C. Herold, 30 N. Michigan, Suite 922, Chicago 60602.

American Hospital Association, [E], Palmer House, Chicago, Aug. 29-Sept. 1. Exec. Vice Pres.: Edwin L. Crosby, M.D., 840 Lake Shore Dr., Chicago 60611.

Black Hills Fall Seminar, Rapid City, S. Dak., Aug. 5-6. Info: John F. Leeds, M.D., 615 Kansas City St., Rapid City, S. Dak. 57701.

National Medical Association (71st Annual Session), Pick-Congress Hotel, Chicago, Aug. 8-12. Exec. Sec.: John T. Givens, M.D., 2400 Corprew Ave., Norfolk, Va.

Rocky Mountain Radiological Society, Brown Palace Hotel, Denver, Aug. 18-20. Sec.-Treas.: Robert W. Lackey, M.D., 4200 E. Ninth Ave., Denver 80220.

Rehabilitation Nursing Course, August 8 through 26, 1800 Chicago Avenue, Minneapolis. Contact: Jean R. Plass, R.N. at the American Rehabilitation Foundation.

National Conference on Infant Mortality, August 12-3, Fairmont Hotel, San Francisco. Contact: AMA in Chicago.

SEPTEMBER

The Annual Fall Meeting of the Northwestern Pediatrics Society will be held on Friday, September 23, at the White Pine Inn, Bayport. Eldon Berglund, M.D. President.

Minnesota Society of X-ray Technologists Annual Meeting, September 30-October 1, Statler Hilton Hotel, St. Paul. Contact: Richard Board, R.T., 416 Marquette Bank Building, Minneapolis.

Second Annual Symposium on Kidney Disease sponsored by the Upper Midwest Chapter of the National Kidney Foundation, St. Paul Hilton Hotel, September 14. Contact: John M. Burns, M.D., 451 North Dunlap, St. Paul.

Scientific Meeting of the Minnesota Society of Anesthesiologists, September 23rd, Place to be determined. Contact: Van Lawrence, M.D., Hennepin County General Hospital, Minneapolis.

Southern Minnesota Medical Association Annual Meeting, September 16, at the Holiday Inn in Austin. Contact: Robert H. Conley, M.D., 304 Belle Avenue, Mankato.

Minnesota State Medical Assistants Society Educational Symposium in Minneapolis, Ambassador Motor-Hotel, September 17th. Contact: Lois Pluckhan, 1553 Medical Arts Building in Minneapolis. Telephone 332-2478.

Methodist Hospital Annual Symposium, September 19 in St. Louis Park. Contact: Hugh A. Edmondson, M.D. at Methodist Hospital.

OCTOBER

Annual Otolaryngologic Assembly Meeting, October 1, Illinois Eye and Ear Infirmary at the Medical Center, Chicago. Contact Department of Otolaryngology, P.O. Box 6998, Chicago.

Hahnemann Medical College Meeting "Theory and Application of Gas Chromatography in Industry and Medicine," October 26-29. Marriott Motot Hotel, Philadelphia. Contact Hahnemann Medical College & Hospital, Philadelphia.

ANNOUNCEMENTS

Minnesota Obstetrical-Gynecological Society Meeting, December 3rd, Hennepin County General Hospital. Contact: Theodore Watson, M.D., 1261 Lowry Medical Arts Building, St. Paul.

How Much Fidelity Bond?

Even with the most trusted employees, and under the most ideal system of internal control, employee dishonesty can and does occur. With a system any less than ideal, an employer may, in fact, be encouraging such dishonesty. It is also a time-worn fact that embezzlements occur in places and at times where they are least expected. The Fidelity and Deposit Insurance Company estimates losses from employee dishonesty at $500,000,000 annually. Thefts range from insignificant amounts up to thousands of dollars, occasionally a sum adequate to bring about complete financial ruin to an employer or firm.

In addition to providing decent working conditions, reasonable hours, adequate wages and opportunity for advancement, employers have a moral obligation to safeguard their employees' integrity by doing everything possible to deter them from yielding to the temptation to embezzle or steal. No system of accounting or internal control has yet been devised which will absolutely guarantee against dishonesty, yet much can be done to keep an inherently honest employee from yielding to temptation in a moment of weakness, or under the stress of financial worry.

Following are some important features of an adequate internal control system. If at least some of these points are not operative in your office, you should discuss them with your management consultant or accountant:

1. Is the mail opened by a trusted employee, *other than* your bookkeeper or cashier?
2. Is a list of mail receipts, classified as to checks, cash or money orders, prepared by this person and checked against the daybook regularly?
3. Are receipts issued for all monies received and are all unused receipts accounted for as they are used or spoiled? Receipts should be serially numbered.
4. Is cash reconciled or balanced daily and subject to check by other than the person responsible for the reconciliation?
5. Are deposits made daily of each day's cash receipts intact and responsibility fixed on one person for making these deposits?
6. Are all overages and shortages reported promptly?
7. Cash withdrawals of any type are potentially dangerous and should not be made. If such withdrawals are made, a voucher showing the amount and the date should be signed by the person receiving the funds.
8. Is cash physically safeguarded to prevent a dishonest employee from blaming "outside theft" in case of shortages?
9. Are the daybook, accounts receivable and patient case histories spot-checked periodically for discrepancies and irregularities?
10. Are all employees handling cash receipts covered by Fidelity Bond or Dishonesty Insurance?

These and other safeguards which can be installed will guarantee *maximum* protection against employee dishonesty, but, as previously stated, cannot guarantee absolute protection.

The fact that employees are covered by fidelity bond, in itself, acts as a deterrent against theft and embezzlement, since it makes the offense somewhat more serious in nature and more likely to be uncovered.

Much has been said about fidelity bond, the next problem is "how much?" After considering the matter thoroughly, we feel that the following simple formula for determining risk exposure is valid and can be used for Dental and Medical offices:

1. 10% of annual gross receipts ....$________
2. 10% of current assets (cash on hand, bank accounts, securities and drug and supply inventories) ....$________

Risk exposure ....$________

The following amounts of insurance should be carried in relation to risk exposure:

Up to $25,000	Equal to Exposure, Minimum $10,000
$25,000 to $125,000	$25,000 to $50,000
$125,000 to $150,000	$50,000 to $75,000
$250,000 to $300,000	$75,000 to $100,000

Remember, no one is immune to employee dishonesty. Your only assurance of maximum protection is a system of adequate internal control, plus bonding of each employee who has access to monies or valuable properties in your office.

William D. Huntington*
Minneapolis, Minnesota

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*Northern Division Manager, Professional Management Midwest.

I have never looked upon ease and happiness as ends in themselves — this ethical basis I call the ideal of a pigsty. The ideals which have lighted my way, and time after time have given me new courage to face life cheerfully, have been Kindness, Beauty, and Truth. — Albert Einstein

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Perspectives

No mariner ever enters upon a more uncharted sea than does the average human being born in the twentieth centry. Our ancestors thought they knew their way from birth through eternity; we are puzzled about day after tomorrow.

— Walter Lippmann

Physician's Diary

Nothing more dangerous than a friend without discretion; even a prudent enemy is preferable. — La Fontaine

Dr. Donald W. Freeman has left the St. Louis Park Medical Center to head up the OB-GYN Department of the Hennepin County General Hospital in Minneapolis.

* * *

Dr. Mario Pliego is the new associate in the department of radiology at the Hennepin County General Hospital, and **Doctors A. MacDonell Richards** and **Gerald Omstad** have joined the Department of Internal Medicine at Hennepin County General Hospital. **Dr. A. MacDonell Richards** is the new assistant chief of that section.

* * *

Dr. James W. Kernohan, emeritus chairman of the sections of pathology of the Mayo Clinic, received the honorary degree of doctor of science from the Queen's University of Belfast, Northern Ireland.

* * *

Dr. George A. Hallenbeck, head of a section of surgery in the Mayo Clinic, has been appointed chairman of the 19 sections of surgery of the Mayo Clinic. Dr. Hallenbeck succeeds **Dr. John W. Kirklin**, who left the Mayo Clinic to become head of the Department of Surgery at the Medical College of Alabama in Birmingham.

* * *

Dr. Harry B. Neel of Albert Lea is the newly elected president of the Minnesota Surgical Society. Other officers are: **Dr. Davitt A. Felder** of St. Paul, vice president, **Dr. Richard C. Lillehei** of Minneapolis and **Dr. W. Spencer Payne** of the Mayo Clinic to the board of directors; and **Dr. Martin A. Adson** of the Mayo Clinic, secretary-treasurer.

* * *

Dr. Lowell L. Henderson, a Mayo Clinic allergist, was elected president of the American College of Allergists at its annual meeting in Chicago.

* * *

Dr. Harold O. Peterson, head of the radiology department at the University of Minnesota Medical School, has been named to the new post of hospital chief of staff.

* * *

NEW LOCATIONS: **Dr. John D. Banovetz** has become associated with **Doctors Conrad J. Holmberg, Robert E. Priest, Harold S. Ulvestad, Robert J. Richard** and **John S. Huff** of Minneapolis . . . **Dr. C. Provence** is now an associate of **Dr. John Savaryn** in the Savaryn Clinic in Waconia . . . **Dr. Gerald R. O'Brien** is the new associate of **Doctors Herbert S. Strait, Bernard W. Lenz** and **Theodore H. Lester** at the Fridley Medical Center in Fridley . . . **Dr. Orville A. Hable** has closed his office in the Buffalo Lake Clinic to return to the Chicago Medical School for further studies . . . **Dr. Robert Splettstoesser** has opened medical offices in the Remsberg Clinic in Tracy . . . **Dr. Charles F. Eisenbeis** of Prairie Village, Kansas, joined the Mankato Clinic in July . . . **Dr. Gerald T. Frane** will join **Doctors George Schissel, James Pattee** and **John Leighton** in Crystal Doctors Park . . . **Dr. Gerald Bigwood** of Hastings has been appointed psychiatrist at the Hiawatha Valley Mental Health Center in Winona.

* * *

Dr. Owen H. Wangensteen was recently given the University of Minnesota's highest recognition to faculty members, that being the new title of Regents' Professor.

* * *

An international symposium on liver disease in honor of **Dr. Cecil J. Watson**, professor and head of medicine at the University of Minnesota's College of Medical Sciences, was held during the month of May. Dr. Watson left the University July 1st after 31 years of teaching, to head a new program in teaching and research at Northwestern Hospital in Minneapolis.

* * *

Dr. William N. Spellacy, medical fellow in OB-GYN at the University, received a $45,000 grant from the Josiah Macy, Jr. Foundation.

Over 2 million mentally retarded people hold jobs. What's the world coming to?

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In fact, if placed in jobs for which they are qualified by special training, 85% of the six million mentally retarded can help support themselves and become productive, efficient workers.

Many employers don't know this yet. Someone ought to tell them.

And for your own information, send for a free booklet. Write to
the President's Committee
on Mental Retardation,
Washington, D. C.

When Ethics and Welfare Programs Clash

*Address by Arnold O. Swenson, M.D.**
First National Congress on Medical Ethics
Chicago, Illinois
March 5, 1966

IN DISCUSSING THE SUBJECT, "When Ethics and Welfare Programs Clash," we must assume that the statement is not merely a rhetorical one but an admission that indeed ethics and welfare programs have clashed in the past and probably will continue to do so in the future.

It has been my privilege to live and practice during the era which saw marked changes in the provision of medical care to the indigent. During the late Twenties the physician cared for this group of individuals as a social duty and with a devotion characteristic of the members of the medical profession.

Hospitalization was provided through county-supported hospitals or through privately-endowed welfare agencies.

As to the cost: the hospitals themselves absorbed a large proportion and prorated it among patients able to pay by averaging the daily cost of hospital care among all its patients.

With the advent of the Depression years and with the medical profession carrying an inordinate financial load in providing medical services for patients unable to pay, local and state welfare programs developed, usually with the aid of the medical profession. Services were provided at reduced cost, but also at minimum compensation to the physician rendering those services.

Section 10 of the AMA Code of Ethics states:

"The honored ideals of the medical profession imply that the responsibilities of the physician extend not only to the individual, but also to society where these responsibilities deserve his interest and participation in activities which have the purpose of improving both the health and the well-being of the individual and the community."

It was in light of this section of our Code of Ethics that the medical profession cooperated, usually with county medical authorities, in developing rules and regulations for the proper care of the medically indigent. These were trying times for the medical profession. We had governmental authorities attempting to keep costs at the lowest possible level and making rules and regulations that would hamstring the doctor in the care of his patients — all resulting in a general lowering of the medical care provided these unfortunate individuals.

Section 6 of the Principles of Medical Ethics states:

"A Physician should not dispose of his services under terms or conditions which tend to interfere with or impair the free and complete exercise of his medical judgment and skill or tend to cause a deterioration of the quality of medical care."

By devotion to the care of the sick and the insistence that the quality of medical care be not sacrificed, many long, tedious and at times frustrating negotiations with governmental authorities resulted.

In general, I believe that the physician's insistence on adequate and good medical care for the medically indigent prevailed, although there was generally a marked decrease in the pecuniary return that the physician received for his services.

There is an old saying that interest does

Continued

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*Duluth, Minnesota.

not bind men together. Interest separates them. There is only one thing that can effectively bind people, and that is a common devotion.

This common devotion of the medical profession, more than any other factor, unified the profession in its insistence that there be no strings tied to the services formed for the indigent patient.

The doctor's devotion or consecration to the care of the sick was accepted by most welfare programs without surprise and without comment, a fact which was in itself a compliment to our group, but at the same time a source of irritation and frustration to our profession, which felt that medicine often had to bear more than its share in the care of the needy sick.

The work of the county or state medical society in its relationship to various welfare programs has had ample guidance from policy statements of the American Medical Association. The last compilation was made in 1965 and brought up to date the various policy statements in reference to the care of the needy sick by the House of Delegates of the American Medical Association, up to and including the December meeting in Miami Beach. These policy statements are familiar to most of you. If not, I suggest that you procure the latest compilation of these policy recommendations.

Now we are faced with new problems associated with the recently-enacted medicare law with its potential influence over the quality and cost of medical care. This includes both the under- and the over-65 segments of our population.

I am sure all of you here are as familiar with the provisions of Public Law 89–97 as I am, and I assume that most of you here sat in on the discussions that were held at both the special session of the House of Delegates in October and the interim session of the House of Delegates in Philadelphia during the past year. Many resolutions were introduced having the same general tone, advising the medical profession not to participate in the implementation of the so-called Medicare Law, although at these same sessions our legal and ethical rights were outlined by the legal counsel for the American Medical Association.

We were told that the Judicial Council has ruled: "Under ordinary circumstances the individual physician, acting independently, is ethically free to select his patients, although under some circumstances the physician's freedom to select his patients may be circumscribed by overriding ethical considerations." These overriding ethical considerations were listed as follows:

1. A physician should respond to any request for his assistance in an emergency.

2. Once having undertaken a case, the physician should not neglect the patient; nor should he withdraw from the case without giving sufficient notice to allow the patient time to obtain another physician.

3. If a physician decides not to participate in the Medicare program or decides to limit his participation, he should so advise the patient in advance of treatment. This applies to services rendered by the physician both in and out of the hospital and to other services provided under the law.

4. As provided in Section 1 of the Principles of Medical Ethics, a physician should not refuse to render medical care to any person if, as a result, such person will be unable to get necessary medical care.

It was also pointed out that a physician should not render services under terms and conditions which tend to interfere with or impair the free and complete exercise of his medical judgment and skill or which tend to cause a deterioration of medical care.

As of the time this paper was written there were no firm regulations regarding the implementation of the Medicare law published by the Department of Health, Education and Welfare. Whether such regulations would be of such a nature as to prohibit participation by an ethical physician in the program remains to be determined.

During the discussions on non-participation I was able to form my own conclusion, based on the language of the law itself, but not on any regulations which the Department of Health, Education and Welfare might promulgate.

I do not believe it would be ethical for me to refuse hospital care or to refuse to certify an over-65-aged patient as needing hospital care if she desires to make use of the hospital benefits under this law. Actually, this certification does not vary a great deal from that required in certifying the necessity for hospitalization under an insurance program.

Hence, I believe it would be unethical for me to refuse to care for this patient in the hospital under the Medicare plan, provided, of course, that the regulations promulgated make it possible for me to give this patient as good care under the Medicare program as it would be if she were to receive care under any other program of hospitalization.

Under the medical insurance program of P. L. 89–97 I also believe it would be entirely ethical for me to receive compensation for my care of this individual under the law, provided I am ethical in making the charges to this individual. It is my intention, and I believe it is the intention of most of the doctors I have talked to regarding this problem, that the patient will be billed directly for my care, as has been the custom in the past. At the present time I do not believe that I could make up my mind regarding the ethics of taking an assignment from the patient and being paid directly by the carrier under government auspices.

This problem, I believe, will be solved when the final regulations adopted by the Department of Health, Education and Welfare are available for our study.

Under Section 9 of our Code of Ethics it states:

"A physician may not reveal the confidences entrusted to him in the course of medical attendance, or the deficiencies he may observe in the character of patients, unless he is required to do so by law or unless it becomes necessary in order to protect the welfare of the individual or of the community."

This question of confidentiality and/or privilege worries all of us. But this question was clarified a great deal to me in an article written by Julia Pearls, LL.B., in the October 1965 issue of the Journal of the New York State Medical Society. In the first paragraph she writes:

"Confidentiality is the disclosure of information imparted under circumstances which are such that the person giving the confidence relies on the nature of the relationship or on an express promise to insure secrecy. No privilege is accorded such a communication. 'Privilege' is a word of art. It is a right to restrain a communication made in confidence from disclosure to anyone under any circumstance. One might say that confidentiality is an ethical principle; privilege is a legal right."

If the regulations promulgated by the Department of Health, Education and Welfare make it necessary for us to divulge confidences without the patient's consent, this would clearly violate our code of ethics.

In conclusion, there has been much public discussion regarding the need for us to modify or to modernize our Code of Ethics in order to make it relative rather than absolute. We are told that we are out of tune with the times, that we are prisoners of our contemporary principles. It has been stated that a sense of history would remind us of the inevitable obsolescence of most principles, the abandonment of which would permit a more imaginative approach to some of the serious problems now facing us. God forbid!

Webster defines "medical ethics" as "moral principles or the morals of an individual action or practice." My imagination is staggered when I try to conceive of a great society of the future wherein morals and principles are fleeting and ephemeral.

I would like to close with this quotation from Henry Van Dyke:

"Four things a man must learn to do if he would make his record true:

"1. To think without confusion clearly;
"2. To love his fellow men sincerely;
"3. To act from honest motives purely;
"4. To trust in God and heaven securely."

Forgetting of a wrong is mild revenge.

FRED, BY SAUNDERS SCHULTZ

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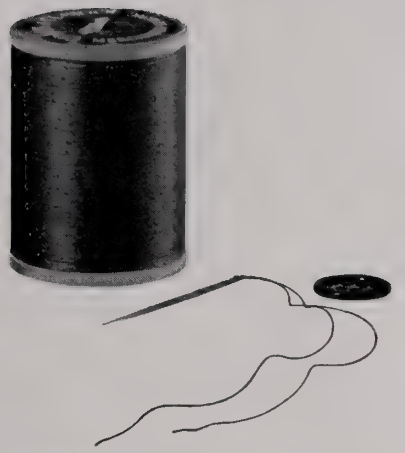

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(1) Portnoy, J.; Brewer, J. and Harris, A.: PUBLIC HEALTH REPORTS, *77:*645-652, August 1962. (2) Joseph, J. M. and Warner, G. S.: A WORKSHOP MANUAL, Md. State Dept. Health, Bureau of Lab., Balto., Md., September 1962. (3) Wollenweber, H. L.: OFF. PATH., *2*, February 5, 1963. (4) Portnoy, J.: MILIT. MED., *128:*414-417, May 1963. (5) Portnoy J.: THE AMER. JOUR. OF CLIN. PATH., *40:*473-479, November 1963. (6) Buck, A. A. and Mayer, H.: THE AMER. JOUR. OF HYG., *80:*85-90, July 1964. (7) Brown, W. J.; Donohue, J. F. and Price, E. V.: PUBLIC HEALTH REPORTS, *79:*496-500, June 1964. (8) Clayton, J. L.; Lindhardt, E. M. and Fraser, R. S.: PUBLIC HEALTH LAB., *22:*206-207, November 1964. (9) Lucatorto, F. M.; Katz, B. D. and Toto, P. D.: THE J.A.D.A., *69:*697-699, December 1964. (10) Portnoy, J.: PUBLIC HEALTH LAB., *23:*43, March 1965. (11) Reed, E. L.: PUBLIC HEALTH LAB., *23:*96-103, May 1965.

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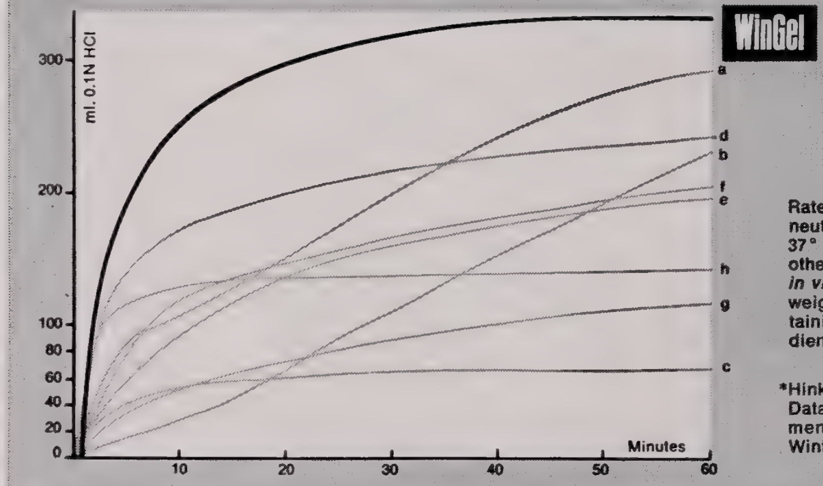

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Anatomy of
Low Back Pain #1
the sedentary life
is often the seat of
low back pain

The human spine is not engineered f prolonged sitting at desks, pianos, typ writers and drafting boards. The stress set up by the heavy, forward-tilted hea and trunk, balanced precariously on a insufficient base, result in strain of th dorsal musculature, particularly at th low lumbar level.

The unusual muscle-relaxant and ana gesic properties of 'Soma' make it esp cially useful in the treatment of low bac sprains and strains. 'Soma' is wide prescribed ☐ **to relieve pain** ☐ **to rel muscles** ☐ **to restore mobility.**

Indications: 'Soma' is useful for management muscle spasm, pain, and stiffness in a variety inflammatory, traumatic, and degenerative musc loskeletal conditions. It also may act to normali motor activity in certain neurologic disturbance

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Precautions: 'Soma', like other central nervo system depressants, should be used with cautio in patients with known propensity for taking e cessive quantities of drugs and in patients wi known sensitivity to compounds of similar chem cal structure, e.g., meprobamate.

Side Effects: The only side effect reported with a frequency is sleepiness, usually on higher tha recommended doses. An occasional patient m not tolerate carisoprodol because of an individu reaction, such as a sensation of weakness. Oth rarely observed reactions have included dizzines ataxia, tremor, agitation, irritability, headache, i crease in eosinophil count, flushing of face, ar gastrointestinal symptoms.

One instance each of pancytopenia and leuk penia, occurring when carisoprodol was admi istered with other drugs, has been reported, as h an instance of fixed drug eruption with carisoprod and subsequent cross reaction to meprobamat Rare allergic reactions, usually mild, have include one case each of anaphylactoid reaction with mi shock and angioneurotic edema with respirato difficulty, both reversed with appropriate therap In cases of allergic or hypersensitivity reaction carisoprodol should be discontinued and approp ate therapy initiated. Suicidal attempts may pr duce coma and/or mild shock and respirato depression.

Dosage: Usual adult dose is one 350 mg. tabl three times daily and at bedtime.

Supplied: Two Strengths: 350 mg. white table and 250 mg. orange, two-piece capsules.

Before prescribing, consult package circular.

for the relief of low back sprains and strain

SOMA

(CARISOPRODOL

Wallace Laboratories, Cranbury, N.J

26S01.

President's Letter

FOR THOSE doctors uncertain of their coronary competence but unwilling to take any of the standard tests, a simple armchair trial is readily available.

Reading, and re-reading with a growing sense of incredulity leading to outrage, the series of articles in the NEW YORKER during late June and July, titled "Annuals of Legislation," subtitled "Medicare," and concluding with a further subtitle, "IV, A Sacred Trust," is a stress situation far more demanding than snow shoveling and grass cutting.

Follow this with a reading of Intermediary Letter #90 from the Bureau of Health Insurance, Department of Health Education and Welfare, "Application of Criteria for Determination of Reasonable Charges."

Conclude, if you can, with the MEDICAL TRIBUNE of July 25, 1966, which carries an interview with Dr. George A. Silver, Deputy Assistant Secretary of Health, Education and Welfare. If you complete these, you may be temporarily an emotional wreck, but your coronaries are functioning well.

The New Yorker series written by Richard Harris is a cynical, distorted attack on the motives behind Medicine's resistance to the passage of Medicare and the bills which preceded it, a more cynical reporting of the political motivations of the supporters of the bill, and an obvious joining by Mr. Harris of the parade of those who attempt to discredit medicine before the public by personal attacks on the sincerity, standards and ethics of medicine's elected leaders and chosen spokesmen. As character assassination, it quite fittingly follows Truman Capote's series on actual assassination, "In Cold Blood," which series ran some weeks earlier.

Most physicians have had experience with Blue Shield and other insurers offering contracts with usual and customary payment for physician services; no difficulties have arisen in these areas. To date, no criteria, no regulations, no sampling, nothing but physician integrity has been required for successful operation. To date nothing but an occasional request for physician-committee decision in unusual cases has been needed to continue that successful operation. No recognition of physician integrity is present in the Bureau of Health Insurance memorandum, nor recognition of physician-developed mechanisms of control. Equally odd, tacit acknowledgement of the quality of medical service appears to be present without question, memorandum or guidelines.

To have Dr. Silver propose in his interview that "if medical students could be channeled to the career goals where the need is greatest" some of our needs could be met in physician placement is regimentation of another type, compatible with centralized planning, acceptable in a Welfare State, and possibly an indication of future governmental involvement in education.

Mr. Harris, ending his series with a quotation from Senator Douglas, finishes "The Doctors of this country say they have a Sacred Trust, I hope they keep it."

How much we as physicians would appreciate the same assurance and performance from these sources.

R P Buckley M.D.

R. P. Buckley, M.D.
President
Minnesota State Medical Association

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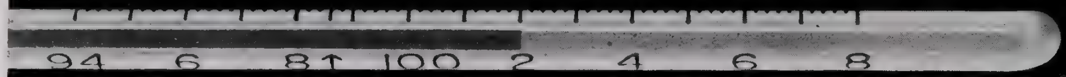

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DOSAGE: *Children under 25 pounds*—5 mg. per pound of body weight every six hours. *Children 25 to 50 pounds*—125 mg. every six hours. *Adults and children over 50 pounds*—250 mg. every six hours. For severe infections, these dosages may be doubled.

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The Anovulatory Syndrome

Treatment with Clomiphene*

W. N. SPELLACY, M.D.**
W. D. COHEN, Ph.D.**
Minneapolis, Minnesota

THE GYNECOLOGIST today is frequently asked to treat the "anovulatory syndrome." This syndrome may present itself in many ways: infertility, amenorrhea, or irregular uterine bleeding. The treatment of this syndrome first requires a specific etiological diagnosis to be made. Since the possible factors which can inhibit ovulation are numerous, one must begin with a complete history and physical examination, including also a complete endocrine evaluation. A large subgroup of patients discovered by this type of study are those with deficient pituitary gonadotropin secretion.

The treatment of patients with low pituitary gonadotropin secretion has gone through four stages of development. The first period covered the years before 1950 when nonspecific treatments were employed, such as estrogen, thyroid, or sedation. Since the treatment was nonspecific, it could not be expected to be very successful and it was not.

The second period occurred in the early 1950s when it was shown that X-ray irradiation of the pituitary gland and the ovary would restore their function in a significant number of patients.[2,3] The mechanism of action was unknown but possibly the increased vascularization following irradiation increased gland function. The suggestion that possible genetic damage could be produced in the patients and transmitted to their progeny discredited this form of therapy. It is rarely used today.

The third period began in the late 1950s and involved the use of exogenous gonadotropin injection with a luteinizing hormone preparation which was readily available in the form of human chorionic gonadotropin. However, a follicle-stimulating hormone was not so easily secured; the first supplies of it were from non-human sources. The problems incurred with these preparations were the production of antibodies to the foreign protein antigen and the lack of patient response due to the species-specific reaction of some hormones.[3] Gemzell and others have subsequently obtained human follicle-stimulating hormone for use and have found it to be effective.[4] The problems involved in its use, however, have been the difficulty and expense of obtaining the hormone, the need for daily injections, and the problem of individualizing dosages.

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*Clomiphene was supplied by the William S. Merrell Company, Cincinnati, Ohio, as Clomid®.

See editorial page 1399.

**From the Department of Obstetrics and Gynecology, University of Minnesota Medical School, Minneapolis, Minnesota.

The fourth period began in 1961, when Greenblatt reported the successful induction of ovulation with Clomiphene.[5] This compound is a nonsteroid, nonhormonal agent which can be clinically synthesized and administered orally.

The purpose of this paper is to present one typical case report of a patient successfully treated with Clomiphene, and to review the action and uses of this drug.

Case Report

A 29-year-old para 1-0-0-1 white female had delivered a normal infant in June 1961. She had not had a menstrual period since that time (33 months) but had had normal menstrual periods prior to that pregnancy. She was seen at the University of Minnesota Hospitals with a complaint of secondary infertility and amenorrhea. The remainder of her history and the physical examination were normal. The laboratory studies included a normal complete blood count, urinalysis, chest x-ray, serology, fasting blood sugar, and serum electrolytes. From the endocrine studies shown on Table 1 it can be seen that all of her endocrine target gland secretions are low. There was no response to the standard Metopirone* pituitary function test (30 mgm/kg. body weight; 4-hour intravenous infusion). A diagnosis of idiopathic hypopituitarism was made and she was treated with Clomiphene. The first three treatment cycles were monitored with basal body temperatures, and on this basis the patient ovulated in each cycle and became pregnant during the third cycle. She had a normal pregnancy and on 10/6/65 spontaneously delivered a 2980-gram normal female infant over an episiotomy using pudendal block anesthesia. She has not menstruated post partum.

Discussion

The action of Clomiphene has been found to be different in experimental animals and in humans. Several investigators have shown the compound to be antiestrogenic and therefore an inhibitor of ovulation in animals.[6] It has also been shown to be toxic to the blastocyst in early pregnancy, thus preventing implantation.[7]

The action of the drug has been extensively studied in humans. There is no direct action on the adrenal gland.[8] The drug is antiestrogenic and produces a decrease in vaginal cornification count and a loss of cervical mucus spinnbarkeit and fern pattern.[9]

The studies of gonadotropin excretion show a rise in luteinizing hormone, follicle-stimulating hormone, and total gonadotropins after treatment.[10] This occurs in both men and women. We now know that the anterior pituitary gland is under the direct control of the hypothalamus which secretes specific polypeptide releasing factors. The hypothalamus in turn is responsive to circulatory estrogen levels, thus closing a negative-feedback loop. Presumably, Clomiphene acts by causing the hypothalamus to secrete gonadotropin-releasing factors which then enter the anterior pituitary gland via the pituitary portal circulation. If there is a normal pituitary, gonadotropin is released into the general circulation, and if normal ovaries are present, they will respond with ovulation.[11]

TABLE I
Endocrine Studies Prior to Clomiphene Treatment

Pituitary		
Sella turcica x-ray — normal		
Follicle stimulating hormone — less than 4 mouse units/24 hours (normal 6-48)		
Thyroid		
Protein bound iodine — 4.0 μgm. % (normal 4-8)		
Cholesterol — 207 mgm. %		
Ovary		
Cornification count — 3% superficial cells		
Endometrial biopsy — inactive proliferative phase		
Adrenal		
Control 24 hour urinary excretion		
17 ketosteroid	6.6 mgm. q.d. (normal 5-15)	
17 hydroxycorticoids	2.4 mgm. q.d. (normal 4-12)	
Plasma Corticoids		
8 a.m.	17.2 μgm. % (normal 5-35)	
8 p.m.	12.4 μgm. %	
ACTH Test (50 units — 8 hours)		
	Pre	Post
17 ketosteroids	5.3	9.6 mgm. q.d.
17 hydroxycorticoid	3.3	25.7 mgm. q.d.
Plasma corticoid	21.6	42.9 μgm. %
Metopirone Test		
	Pre	Post
17 hydroxycorticoids	4.1	3.9 mgm. q.d.

---

*Metopirone was supplied by Ciba Pharmaceuticals Company, Summit, New Jersey.

Clomiphene has been used for the treatment of many conditions, including irregular menses, endometrial hyperplasia, amenorrhea, infertility, precocious puberty, Stein-Leventhal syndrome, carcinoma of the endometrium, cystic mastitis, galactorrhea, and oligospermia.[11]

The success in producing ovulation has been approximately 70% in those patients who have an intact pituitary gland and ovary. The pregnancy rate is approximately 23%.[12]

The side effects incurred by using this drug are dose-related. Few of them are serious. They include hot flashes, blurry vision, ovarian cyst formation, nausea and vomiting, vertigo, mittelschmerz, and alopecia.[11]

The drug is given orally and the usual dosage is 50 mgm. twice each day for five days every month. Patients should be examined between each treatment period.

Conclusion

With Clomiphene, the gynecologic endocrinologist has a new effective therapeutic tool with which to treat the "anovulatory syndrome."

Acknowledgment

The authors wish to express their appreciation to Dr. John E. Johnson, Jr., of the William S. Merrell Company for his generous supply of Clomid.

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IT'S THE LAW*

Physicians, surgeons, nurses, pharmacists and hospital officials are required to notify police whenever they come upon injuries that appear to have arisen from mistreatment of youngsters under 16 years of age. This will better identify children in danger so that they may be protected. The law is not to punish parents although criminal action may result in some instances. Such reporting is mandatory and allows the protective services throughout the State to be brought to bear in an effort to protect the health and walfare of these children and to prevent further abuses.**

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*Minnesota Statutes 1961 Sec 626.52 — Sec 2 as amended.

**See Neuro-Pediatrics Conference page 1429.

Above all things, keep clean; it is not necessary to be a pig in order to raise one.

— Robert Ingersoll

Efficaciousness in Proportion to Cost

About a generation ago, it was suggested by some of the pharmacologists that certain of the salts of lithium, especially when taken in the diluted form in which they occurred in natural waters and medicinal springs, were of very great value for the cure and prevention of the formation of calculi in the human body.

The lithium and lithia springs throughout the country followed up this popular persuasion of curative value with properly suggestive advertising, and lithium waters were consumed by the hundreds of thousands of gallons every year. Then the government became interested in the question of pure food and drugs and made a careful analysis of these so-called natural lithium waters. It was found that so far as some of the most famous of them were concerned there was more lithium in the Potomac as it flowed by Washington than there was in the much advertised and much consumed natural lithium water. It was found further that the Potomac was not particularly rich in lithium and that it would probably take some thousands of gallons, at least, of Potomac water to provide what would ordinarily be considered a single reasonable therapeutic dose of lithium.

The one really efficacious factor in this lithium water was not the lithium but the water. . . . Those who were relieved in any way, however, were quite sure it was the lithium that was effecting its beneficent work. . . . Water is too cheap to cure most people. The rich man at Rome complained to Galen that he could not be cured by these drugs that were so cheap that even the poor could obtain them to cure themselves and he must have something more expensive for that purpose, for surely the remedy would be more efficacious just in proportion to the increased amount of money that he had to pay for it.*

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*Walsh, James: Cures. D. Appleton & Co., New York, 1924.

Medical Men on Postage Stamps

Hippocrates (c. 460-357 B.C.), celebrated physician of antiquity and known as the Father of Medicine, was a native of the Island of Cos where he practiced and taught medicine, elevating the medical school there to a high degree of excellence and eminence. To him is credited the Hippocratic Oath. Greece issued a postage stamp in his honor in 1947.

Derivatively Speaking

Impetigo—from Latin *impetere* (to attack)

The Tobacco Tyrant

Having read so much about the bad effects of smoking he decided to give up reading.

From Jacob Braude's "Speaker's Encyclopedia"

Mechanical Large Bowel Obstruction

Simulating Paralytic Ileus

CLAUDE V. DESHAZO, M.D.*
CHARLES A. MURRAY, M.D.*
RAYMOND C. BONNABEAU, JR., M.D.*
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THE USE OF routine x-ray studies of the abdomen has been invaluable in permitting the early diagnosis of both small and large bowel obstruction when the clinical findings are equivocal. The following communication concerns two cases of mechanical large-bowel obstruction in which three competent radiologists and the responsible physicians were led to a diagnosis of paralytic ileus by the clinical picture and the radiologic findings.

Case Reports

Case 1:

A 36-year-old woman was admitted to the surgical service because of unrelenting abdominal distention of four days' duration. The patient, who was unable to give any history, had had no prior abdominal operations and had received several enemas before referral in an effort to reduce this distention. Vital signs were normal while physical examination revealed only moderate abdominal distention and the absence of bowel sounds. Digital rectal examination and routine laboratory studies were normal.

Radiographic studies of the abdomen were interpreted as showing a large amount of gas in the colon with some in the small bowel (Figure 1-a). The fluid levels seen in the colon in the upright film (Figure 1-b) were felt to be due to the multiple enemas the patient had received previously. The films were considered to be compatible with a paralytic ileus.

Proctoscopy to 25 cm. revealed no lesions. No gas or fluid was expelled during the examination. An emergency barium enema (Figure 1-c) revealed a caecal volvulus. Exploratory laparotomy confirmed the diagnosis.

Case 2:

A 63-year-old woman was admitted to the surgical service because of a symptomatic hiatus hernia. Physical examination was unremarkable, and on the eighth hospital day a vagotomy, pyloroplasty, and hiatus herniorrhaphy were performed. On the seventeenth postoperative day the patient was noted to have abdominal distention with an absence of bowel sounds.

On the basis of the physical findings and a dilated colon on the abdominal x-rays (Figure 2-a) a diagnosis of paralytic ileus was made. The abdominal distention did not relent with nasogastric suction and a sigmoidoscopy revealed no lesions and yielded no gas or fluid. A barium enema demonstrated obstruction at the splenic flexure of the colon (Figure 2-b), which subsequently was found at operation to be due to an adhesive band.

---

*Department of Surgery, University of Minnesota Hospitals, Minneapolis, Minnesota.

Comment

These two cases represent instances in which the establishment of a diagnosis of mechanical large bowel obstruction was delayed because the radiographic picture was interpreted as being consistent with paralytic ileus. Both patients failed to present the classical physical findings and symptoms of mechanical obstruction, namely, hyperactive bowel sounds, rushes, and cramping abdominal pain.

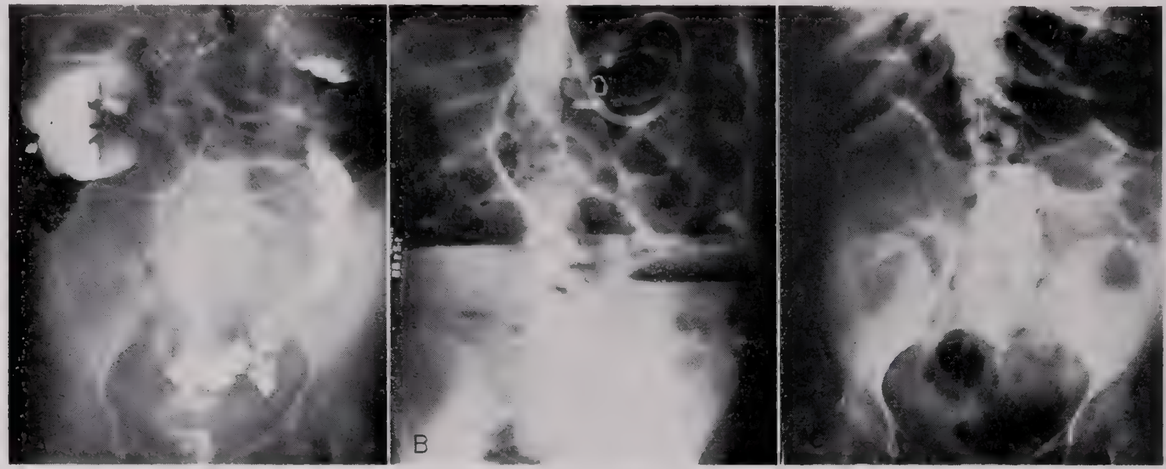

Fig. 1 — This 36-year-old woman (Case 1) was admitted to the hospital with a four-day history of abdominal distress. (a-left) A photograph demonstrating a caecal volvulus in the right upper quadrant as seen on barium enema and confirmed at the time of surgery. (b-middle) A photograph of an upright film of the abdomen illustrating fluid levels in the colon attributed to multiple enemas the patient had received prior to admission. (c-right) A photograph of the initial flat plate of the abdomen showing distended loops of the large and small bowel.

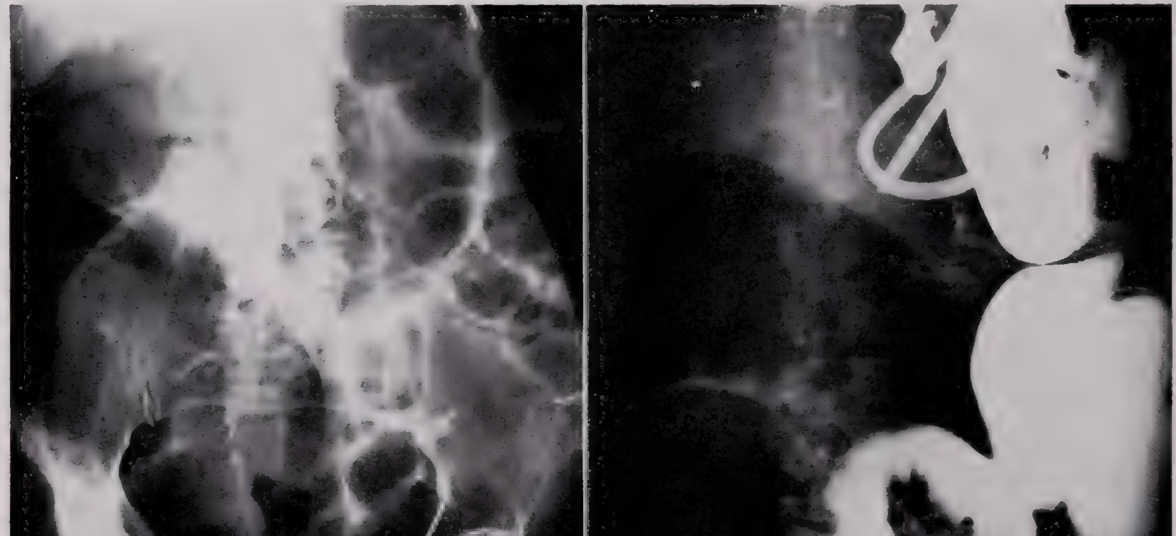

Fig. 2 — (a-left) A photograph of the abdominal x-ray in Case 2 taken on the seventeenth postoperative day after a vagotomy, pyloroplasty and hiatus herniorrhaphy were performed. The film shows distended loops of colon without fluid levels. (b-right) A photograph demonstrating the site of obstruction at the splenic flexure of the colon found by barium enema. This obstruction was found to be due to an adhesive band at the time of re-operation.

The radiographic differentiation between mechanical and paralytic ileus is characteristically based not only on the presence of air-fluid levels, but also on the absence of air distal to the point of obstruction. In both of the cases presented these clear-cut radiographic manifestations were missing. In Case 1 the utilization of enemas prior to the radiographic examination further confused the issue due to the introduction of air and fluid into the large bowel.

In cases of unrelenting bowel distention where the colon is distended but x-ray findings are equivocal or even give the appearance of paralytic ileus, the use of sigmoidoscopy and barium enema is of extreme importance. If facilities for barium enema are not available initially, sigmoidoscopy will generally reveal normal colon and no gas or fluid in the distal bowel if there is a mechanical obstruction. Barium enema can then be obtained to delineate the obstructed area in the colon.

Summary

Flat and upright radiographic studies of the abdomen are a valuable diagnostic tool and are used extensively to differentiate between paralytic and mechanical ileus. The early use of both sigmoidoscopy and barium enema in these two cases was necessary to establish a diagnosis. In cases of unrelenting abdominal distention due to mechanical large-bowel obstruction, where the radiographic picture appears compatible with a paralytic ileus, the use of these procedures may be lifesaving.

Medical Men and Music

Apollo and Aesculapius

Music exalts each Joy, allays each Grief,
Expells Diseases, softens every Pain,
Subdues the rage of Poison, and the Plague;
And hence the wise of ancient days adored
One power of Physic, Melody, and Song.

In the Greek and Roman pantheon Apollo, god of music and healing, and his son and pupil Aesculapius, god of medicine, were jointly venerated as divine practitioners of sister arts. In the iatro-philosophy of the ancients disease was the result of spiritual and, by extension, physical disharmony with the grand systole and diastole of Nature. Restoration of health therefore required the resynchronization of the vibration of the human soul with that of the anima mundi.* Hence the iatromantic therapy of the Greeks and Romans — employing music as a reciprocal psycho-iatric and physico-iatric agent.

Sometimes music was used in conjunction with other prophylactic measures. Pythagoras' psychobiosis featured a combination of music and diet; and Homer recounts that when Ulysses hemorrhaged from a wild boar gash, attendants first bandaged the wound and then chanted a song of healing thereon.

But generally music alone sufficed. Cato relied on ancient songs to heal sprains and Varro to relieve gout. Herophilus of Alexandria was reported to have successfully treated disease by regulating his patients' pulses according to the particular musical scale he considered most appropriate in each individual case. Especially responsive to the melodious tones of the flute were ischialgia, lumbago, snakebite, and insanity.

And after all did not Saul's profound melancholia vanish at the sound of David's harp?

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*See Test Your Word Score, Page 1411.

Mikulicz' Syndrome

This syndrome consists of bilateral painless enlargement of the salivary and lacrimal glands, accompanied by dryness of the mouth and decreased or absent lacrimation. Mikulicz first described the condition in 1892. Schaffer and Jacobsen in 1927 reviewed the subject comprehensively and offered an etiologic classification.

The localized glandular enlargement is usually a manifestation of a generalized disease process. In most cases the causative factor has been found to be either tuberculosis, leukemia, lymphosarcoma, or sarcoidosis. In one group reported by Radding, 24 out of 38 cases were associated with leukemia. Diagnosis may often be facilitated by study of the bone marrow.

Rubin and Besse have suggested a differentiation between the terms "Mikulicz' syndrome" and "Mikulicz' disease." They state that in the syndrome roentgenographic studies of the parotid gland show a normal branching duct system with complete evacuation of contrast medium during the emptying phase, whereas in Mikulicz' disease there is sialectasis or dilatation of the terminal ducts that may become cystic. The course is variable, usually chronic, and recurrences are frequent. Treatment depends upon the etiologic factors. If a blood dyscrasia exists, specific measures should be used. Surgical excision and irradiation of the salivary glands have been done. If biopsy supports the diagnosis of sarcoidosis, hydrocortisone therapy may yield favorable results.

Durham, Robert H. — Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

Oliver Wendell Holmes on Know-How

Book-knowledge, lecture-knowledge, examination-knowledge, are all in the brain. But work-knowledge is not only in the brain, it is in the senses, in the muscles, in the ganglia of the sympathetic nerves,—all over the man, as one may say. . . . See a skillful surgeon handle a broken limb; see a wise old physician smile away a case that looks to the novice as if the sexton would soon be sent for; mark what a large experience has done for those who were fitted to profit by it, and you will feel convinced that, much as you know, something is still left for you to learn.

The Mona Lisa

Hers is the head upon which all the ends of the world are come, and the eyelids are a little weary. It is a beauty wrought out from within upon the flesh, the deposit, little cell by little cell, of strange thoughts and fantastic reveries and exquisite passions. . . . All the thoughts and experience of the world have etched and moulded there, in that which they have of power to refine and make expressive the outward form, the animalism of Greece, the lust of Rome, the mysticism of the middle age with its spiritual ambition and imaginative loves, the return of the Pagan world, the sins of the Borgias. She is older than the rocks among which she sits; like the vampire, she has been dead many times, and learned the secrets of the grave; and has been a diver in deep seas, and keeps their fallen day about her; and trafficked for strange webs with Eastern merchants; and as Leda, was the mother of Helen of Troy, and, as Saint Anne, the mother of Mary; and all this has been to her but as the sound of lyres and flutes, and lives only in the delicacy with which it has moulded the changing lineaments, and tinged the eyelids and the hands.—Walter Pater

Gangrene of the Foot Following Operation

Lumbar Sympathectomy*

M. J. LOEB, M.D.**
Y. SAKO, M.D.**
Minneapolis, Minnesota

TRULY DRAMATIC improvement in circulation in patients with arterial occlusive disease is obtainable by direct arterial reconstructive surgery, but the limiting factor has been that only 15 to 20% of patients with femoropopliteal occlusive disease are suitable candidates for reconstructive operations. For the remaining large group of patients the only surgical consideration is that of lumbar sympathectomy as an adjunct to medical management.

Lumbar Sympathectomy

Lumbar sympathectomy for ischemia of the extremities has been performed for forty years, and it is common knowledge that skin circulation is markedly improved in those that respond favorably to sympathectic denervation; whereas improvement in circulation to the muscles is not to be expected. Nevertheless, nearly every reported series of lumbar sympathectomy will record 20 to 30% of the patients as having increased walking distance postoperatively.

Variable Response

Individual response to lumbar sympathectomy varies; at one time detailed studies were performed in an attempt to select those that might respond favorably. Experience has shown that preoperative tests could not be relied upon for accurate prediction; therefore our tendency has been to recommend lumbar sympathectomy to all patients except those with advanced disease such as gangrene no longer limited to the digits or in patients with overall general poor health. Liberal indications for recommending lumbar sympathectomy have also been prompted by the desire to offer the patient the potential benefit of improvement or limb salvage. Also, the mortality attending the operation has been low — less than 1% in over 400

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*Measurements reported herein are from a study supported by Grants from the American Heart Association.

**Department of Surgery, Veterans Administration Hospital and the University of Minnesota, Minneapolis, Minnesota.

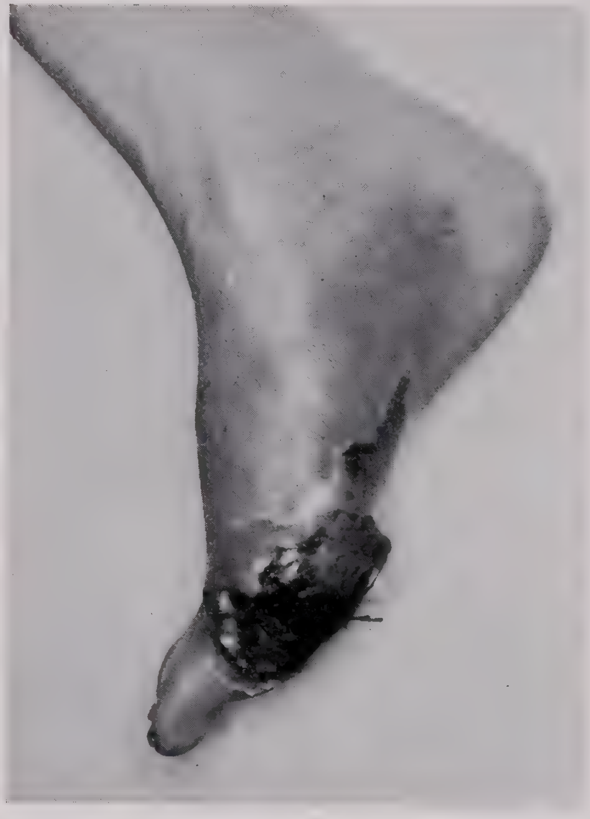

Fig. 1 — Extent of progression of gangrene at time of amputation.

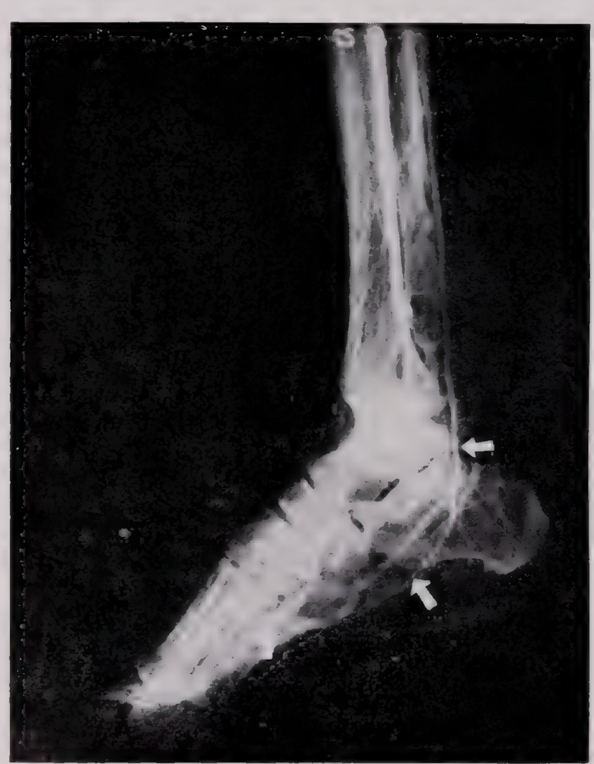

Fig. 2 — Angiographic study of amputated specimen showing patent posterior tibial artery (arrows).

lumbar sympathectomies over a ten-year period.

Low-Risk Complications

The commonest postoperative complaint is that of postsympathectomy neuralgia, which occurs in 20 to 25% of patients. Other than the neuralgia being secondary to the procedure of sympathectomy, the etiology is somewhat obscure. Fortunately, the difficulty is self-limited to about six weeks. Another complication is that of disturbance in male sex function if bilateral lumbar sympathectomy includes the first lumbar segment. This complication can be avoided by not disturbing the first lumbar ganglion on one side.

Paradoxical Response

Another complication of lumbar sympathectomy, which is quite infrequent but rather striking when it does occur, is that of aggravation of the ischemic symptoms and findings shortly after sympathectic denervation. This has been called a "paradoxical" response. Atlas[1] in 1942 was the first to call attention to this phenomenon; he reported on three patients who had onset of pedal gangrene shortly after lumbar sympathectomy. Baffes et al.[2] also describe three cases felt to represent a "paradoxical" response to sympathectomy. Other investigators[3] have discussed clinical situations where this is likely to occur.

Case Report

A 67-year-old mildly diabetic man being treated for congestive failure and pneumonia was seen in consultation because of severe ischemia of the right foot. Examination revealed an ulcer 2 x 3 cm. on the large toe. The foot showed no edema. Femoral and popliteal pulses were strong bilaterally but there was no pedal pulse. Treatment consisted of continued bed rest and foot soaks; but after four weeks with no improvement a right lumbar sympathectomy removing ganglions L_2 to L_4 and an amputation of the toe at the metatarsal-phalangeal joint were done. Postoperatively the right upper leg became warmer. Both femoral and popliteal pulses were present and of the same quality as before surgery, but there was rapid progression of the gangrene beginning at the amputation site and spreading proximally to involve the distal medial aspect of the foot (Figure 1). Because healing appeared extremely remote, an amputation was done below the knee. The latter site was chosen because the patient continued to have a strong popliteal pulse, although at the site of amputation the artery was blocked. The amputation site healed primarily.

An angiographic study was made of the amputated limb. This showed occlusion of the anterior tibial and peroneal arteries, whereas the posterior tibial artery was open (Figure 2). The distribution of this artery includes part of the gangrenous area of the foot. The arteries in the area of the gangrene appeared patent (Figure 3).

Discussion

Since there was no apparent progression of the gangrenous changes before sympathectomy, the rapid spread of the necrosis after operation was quite striking and it appeared that there was some causal relationship. Sympathetic denervation of the right leg was apparent because the right thigh and upper lower leg were warmer than preoperatively and the right side was warmer than the left. These observations suggest that acceleration of gangrene was precipitated by shunting of blood from areas distal to the arterial obstruction.

Pressures and flow measurements after lumbar sympathectomy have been made and previously reported.[4] Lumbar sympathectomy provoked an increase in blood flow in the artery proximal to the obstruction; thus in femoropopliteal occlusion flow in the common femoral artery increases following lumbar sympathectomy. There was, however, a fall in pressure in the arterial bed distal to the point of obstruction (Figures 4 and 5). As illustrated in Figure 5, the common femoral artery pressure is 168/104 and the popliteal artery pressure, 68/60. Ten minutes after denervation popliteal artery pressure fell to 36/32. All pressures were direct arterial measurements. This suggests that although lumbar sympathectomy increases the total blood flow to the affect limb, certain areas may actually have a lower tissue perfusion pressure, which may explain the aggravation of the ischemia. With fall in pressure and consequent stasis, arterial occlusion may occur. The fall in pressure undoubtedly is temporary and may actually provoke increase in collateral blood vessel formation, because such vessels tend to form between areas of greater gradient. This may explain why benefits from lumbar sympathectomy occur gradually over a period of up to one year. Although it is difficult to select those

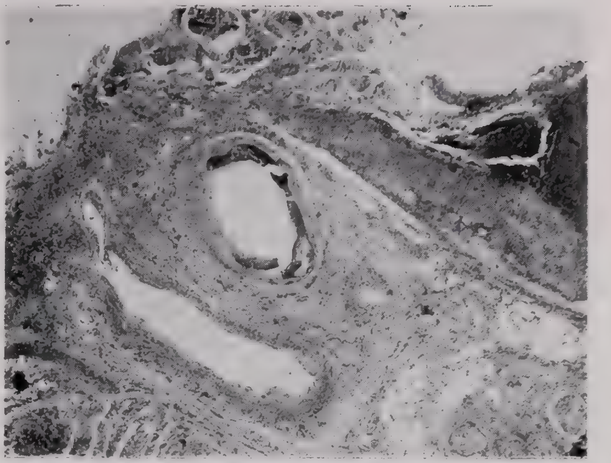

Fig. 3 — Histologic section (x12) taken at level of ulcer showing patent vessels with surrounding gangrenous changes.

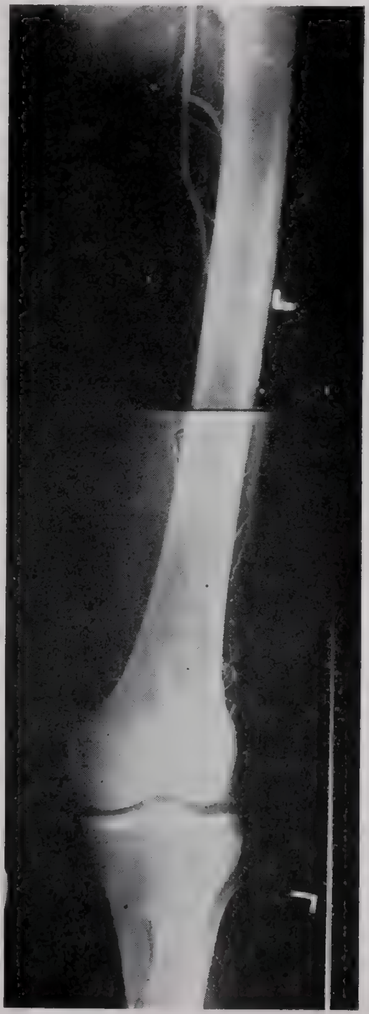

Fig. 4 — 60-year-old male with intermittent claudication. Angiogram shows femoropopliteal artery occlusion. Sympathectomy increased blood flow in the common femoral artery from 140 to 300 cc. mean flow per minute 10 minutes after the nerve section.

patients who may respond adversely, it would appear that those with severe ischemia may be the ones to have aggravation of the ischemia since they could not tolerate a temporary fall in pressure in the area distal to the obstruction.

Summary

A discussion has been presented of a patient who appears to represent an example of a paradoxical response following lumbar sympathectomy. In previous studies, pressure measurements following lumbar sympathectomy suggest that hemodynamic changes may account for aggravation of ischemia following operation. If the immediate effect is not detrimental, it would appear that the fall in pressure would stimulate collateral blood vessel formation.

Since the occurrence of the so-called paradoxical response is infrequent, withholding operation on this basis alone would deprive a great number of patients of the potential benefits from lumbar sympathectomy. At the same time, in patients with advanced disease this hazard ought to be kept in mind.

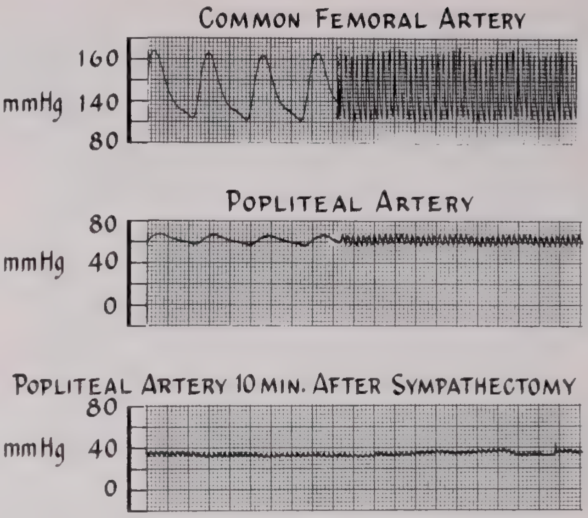

Fig. 5 — Direct arterial pressures in patient described in Figure 4. There was a 53% fall in popliteal artery pressure ten minutes after lumbar sympathectomy.

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Gulliver's Travels—the Ruling Yahoo*

"The leader had usually a favorite as like himself as he could get, whose employment was to lick his master's feet and posteriors, and drive the female Yahoos to his kennel; for which he was now and then rewarded with a piece of ass's flesh. This favorite is hated by the whole herd; and therefore to protect himself, keeps always near the person of his leader."

—Heritage Press 1940

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*See Minnesota Med 49:1080, 1966.

Tolerance

We are in favor of tolerance, but it is a very difficult thing to tolerate the intolerant and impossible to tolerate the intolerable. — George Prentice

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I have never discarded beliefs deliberately. I left them in the drawer, and, after a while, when I opened it, there was nothing there at all. — William Sumner

Mitral Stenosis*

Functional and Clinical Manifestations

JAMES N. KARNEGIS, M.D.**
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THE PURPOSE of this paper is to relate the functional and clinical manifestations of mitral stenosis to the underlying anatomic and pathologic states.

Basic Considerations

Mitral stenosis is a form of obstruction to pulmonary venous outflow. Impairment of pulmonary venous outflow can also occur at other levels, either upstream or downstream to the mitral valve, and mitral stenosis shares hemodynamic findings with these other obstructive conditions.

The fundamental disturbance in mitral stenosis is an impediment to the forward flow of blood. The resultant effect of this abnormality can best be related to the degree of the stenosis, that is, to the area of the mitral valve orifice. The normal mitral valve has an orifice of about five square centimeters. It is generally agreed that this area must be reduced to about twenty per cent of normal or one square centimeter before significant benefit can result from surgical alleviation of the stenosis. It is obviously important not only to diagnose the presence of mitral stenosis but also to determine the severity of the obstruction.

The area of a stenotic mitral valve can be translated into functional equivalents. This requires consideration of the magnitude of the flow of blood through the mitral valve and the pressure gradient producing that flow. The interaction of these three variables can be appreciated from the statement that the amount of flow through the mitral valve in diastole is proportional both to the pressure gradient across the valve and to the valve orifice area. Gorlin and Gorlin[1] have indicated this interrelationship in a useful equation:

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$$MVA = MVF/31\sqrt{Pa-Pd}$$

where MVA = mitral valve area
MVF = mitral valve flow
Pa = mean left atrial pressure
Pd = left ventricular mean diastolic pressure
31 = a constant.

From this equation one can see the hemodynamic consequences of mitral stenosis. If the MVA is reduced, a greater pressure gradient is required to maintain the same cardiac output. If the pressure gradient does not increase, the cardiac output must decrease as the severity of the stenosis increases. The severity of mitral stenosis cannot be interpreted from pressure studies alone in patients with congestive heart failure, since the pressure gradient may not be impressive in the face of a low MVF. It is therefore clear that the physiologic assessment of mitral stenosis requires not only knowledge of the pressure gradient but also a simultaneous measurement of the flow through the valve.

In the formula of Gorlin and Gorlin the pressure gradient factor is expressed as a square root, which means that a given change in either the MVA or the MVF alone produces an effect in the pressure gradient of a magnitude related to the square of that change.

Physical Examination

Some patients with mitral stenosis have a peculiar facial coloring. This is especially seen in the cheeks as a dusky-reddish malar flush. Those with a low cardiac output may show cyanosis due to peripheral blood oxygen desaturation. In the presence of pulmonary emboli and pulmonary infarction jaundice may supervene, especially if hepatic congestion coexists.

Cardiac Size

The over-all cardiac size may not be increased in pure mitral stenosis, but palpation will usually reveal a left parasternal heave indicating right ventricular hypertrophy. One may also be able to palpate an opening snap and an apical diastolic thrill.

First Heart Sound[2]

The first heart sound is associated with closure of the mitral valve. With stenosis of the mitral valve there is a tendency for the amplitude of the first heart sound to be increased and for the onset of the sound to be delayed in relation to the beginning of the simultaneously recorded QRS complex of the electrocardiogram.[3]

The delay in the onset of the first heart sound can be explained by the presence of an elevated left atrial pressure. A longer period of time is required during systole for the left ventricular pressure to rise to equal and exceed the high left atrial pressure and thus to close the valve. The elevated left atrial pressure together with the fibrous and other physical changes in the mitral valve resulting from the rheumatic disease can account for the loud first heart sound associated with closure of the valve. These same factors can also explain at least in part the presence of an opening snap, the noise produced in these patients by the normally inaudible opening of the mitral valve.

There is no systolic murmur in pure, isolated mitral stenosis. A pansystolic murmur may be heard, however, when tricuspid insufficiency is also present. This murmur is quite similar to that of mitral insufficiency and thus may suggest a mixed mitral lesion. Therefore, finding a pansystolic murmur

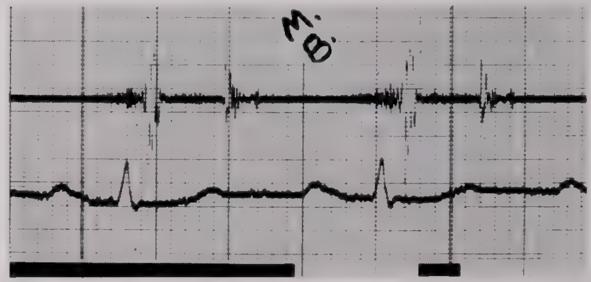

Fig. 1 — Phonocardiogram of a patient with severe mitral stenosis.
Upper tracing: Low frequency phonocardiogram taken at the apex. A crescendo presystolic murmur ends in a very loud first heart sound. In diastole an opening snap follows the second heart sound.
Lower tracing: Simultaneous recording of lead II of the electrocardiogram.

does not exclude the presence of pure mitral stenosis, since the cause may be tricuspid rather than mitral reflux.

Stenosis of the mitral valve affects both components of the second heart sound. The low cardiac output is probably responsible for the relatively quiet first or aortic component of the second heart sound which is produced by closure of the aortic valve. The pulmonary hypertension accompanying left atrial hypertension produces the accentuated second or pulmonic component of the second heart sound which occurs with closure of the pulmonic valve.

Opening Snap

As described above, an opening snap follows the second heart sound in mitral stenosis, tending to move progressively closer to the second sound as the stenosis becomes more severe. This finding together with time measurements of the first heart sound as discussed above has been used by Wells as a phonocardiographic index of the severity of mitral stenosis.[3]

Diastolic Murmur

When the cardiac rhythm is sinus, patients with mitral stenosis may exhibit a low-frequency, rumbling presystolic murmur and also a mid-diastolic murmur following the opening snap, both murmurs produced by the development of turbulence in the blood as it is forced through the narrowed valve. The palpatory phenomenon of a loud mitral rumble is a diastolic thrill.

The diastolic murmurs of mitral stenosis may be lost under two different conditions. First, the presystolic murmur disappears when the rhythm changes from sinus to atrial fibrillation, since the presystolic component depends on atrial contraction. Second, both the mid-diastolic and the presystolic mitral murmurs may be absent in the patient with congestive heart failure, the flow through the narrowed orifice being insufficient to generate the murmurs. These are the instances of so-called silent mitral stenosis. The murmurs may reappear, however, when compensation is regained and the cardiac

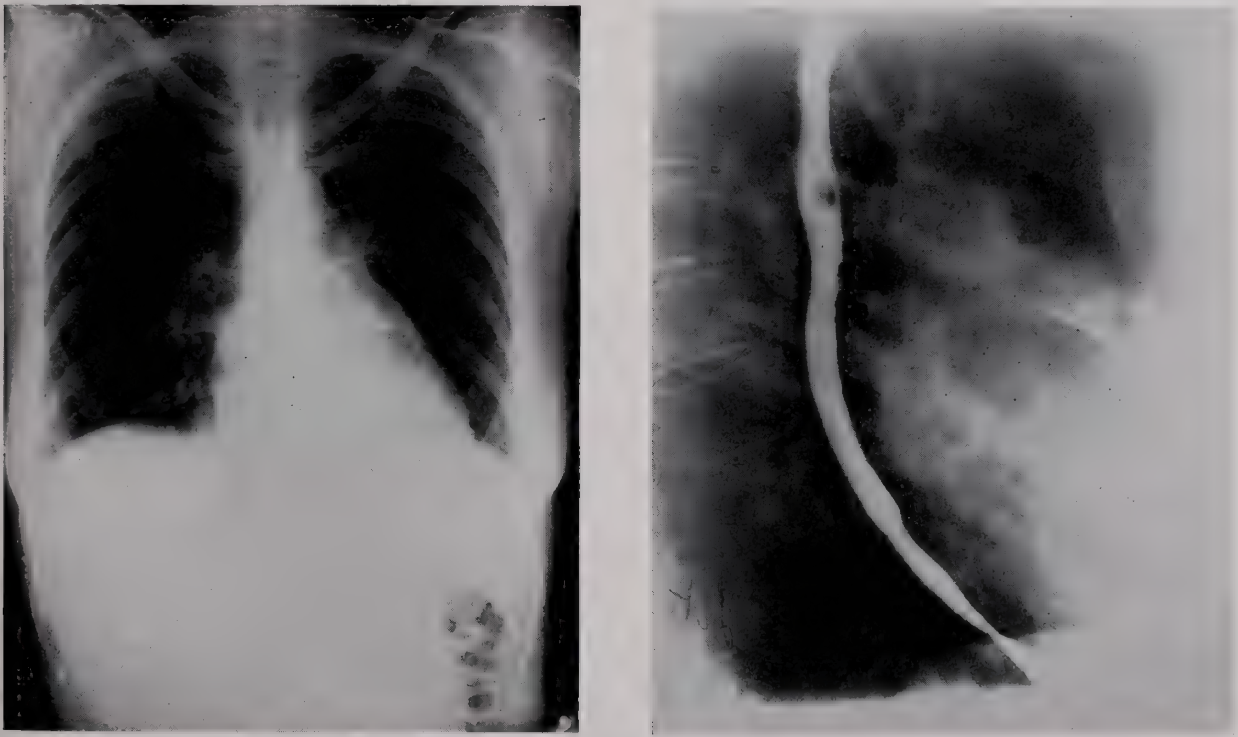

Fig. 2 — Thoracic roentgenograms of a patient with mitral stenosis. Left: posteroanterior view. The left atrial appendage can be seen along the left cardiac border. A double density is visible due to the left atrium which is enlarged and elevating the left mainstem bronchus. Right: lateral view. The enlarged left atrium is displacing the barium-filled esophagus posteriorly.

output improved.

Figure 1 shows the phonocardiogram of a patient with proved isolated mitral stenosis. The tracing illustrates several of the auscultatory events discussed above.

Roentgenographic Findings

Chest roentgenograms also reflect the derangements which occur in mitral stenosis. The increased left atrial pressure is accompanied by enlargement of this chamber. The enlarged left atrium can often be discerned on the posteroanterior film but is usually better seen on the lateral and right anterior oblique projections. The enlarged left atrium may displace the esophagus and elevate and compress the left main stem bronchus. Horizontal septal lines may be visible, particularly in the costophrenic areas. These lines are Kerley's B lines and indicate the presence of high pulmonary venous pressure. The pulmonary artery and right ventricle share in the pressure elevation present throughout the lesser circulation. The roentgenograms will disclose the resultant dilated central pulmonary arteries and the enlarged right ventricle. Figure 2 demonstrates some of the typical roentgenographic features found in a patient with mitral stenosis.

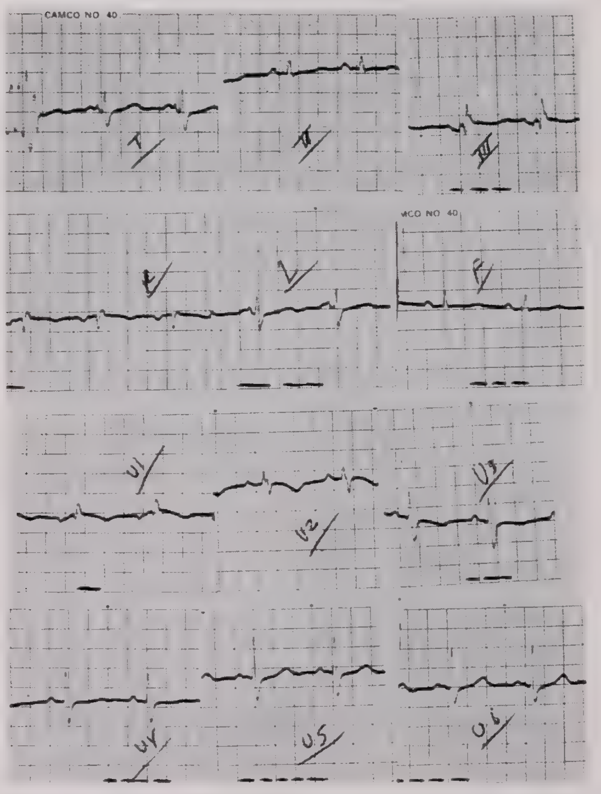

Fig. 3 — Electrocardiogram of a patient with mitral stenosis. The P waves are broad and notched. There is right axis deviation, a qR complex in V_1, and an Rs complex in V_6. The tracing is considered typical of that seen in mitral stenosis.

Electrocardiographic Findings

The electrocardiogram may show some characteristic features in mitral stenosis, as shown in Figure 3. The enlarged left atrium may cause the P wave to be notched in the limb leads and to have a broad, deep negative terminal deflection in lead V_1. In some cases the electrocardiogram may show evidence of right ventricular hypertrophy. It has been our experience, however, that the electrocardiogram in mitral stenosis not infrequently fails to be diagnostic.

Complications

The complications of mitral stenosis can often be explained by the underlying basic disease. If the pulmonary venous and pulmonary capillary pressures rise above a critical level, *pulmonary congestion* and edema ensue. The pulmonary vascular hypertension may result in *hemoptysis,* the bleeding point often being ruptured bronchial veins. *Lung infections* are probably encouraged by pulmonary congestion and compressed bronchi. Pressure on the left recurrent laryngeal nerve can cause *hoarseness.* If the pulmonary hypertension is extreme, the main pulmonary artery may become so dilated that the pulmonic valve becomes incompetent. The pulmonic insufficiency then produces the basal diastolic murmur known as the Graham-Steell murmur.

Patients with mitral stenosis are predisposed to *embolization* for at least two reasons. One is chronic left atrial and pulmonary congestion and engorgement; the second is the not infrequent complication of atrial fibrillation. Both factors act in setting the stage for embolization, either pulmonary or systemic.

Pulmonary emboli occur more frequently in mitral stenosis than is generally appreciated. Certainly a rapid progression of pulmonary hypertension and right ventricular hypertrophy with strain should alert one to the possibility. The diagnosis of pulmonary emboli can be difficult; diagnostic or even suggestive features may be absent in the electrocardiogram and chest roentgenogram until late in the course of the disease.

Systemic emboli may occur with dread effects. Emboli to the brain, kidneys and limbs are not rare. Mitral stenosis should be sought for and must be ruled out when a relatively young person suffers a cerebrovascular accident. Embolization can cause havoc in a person whose basic disease, mitral stenosis, may be amenable to surgical treatment.

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Buckle Up

Plan Your Trip

Freeway driving leaves little time for decisions and offers little opportunity to retrace steps. Study highway maps and decide which entrance and exits you will use and where you will stop for food and fuel. And WATCH for your exit.

Know your route to the freeway, the interchange where you leave, and the route from that interchange to your destination.

Know where you will stop. Controlled access is the key to modern highways, but it means that service stations, restaurants, and motels will be available only by leaving the freeway.

Know freeway speed limits and laws.

Get Plenty of Rest Before Starting a Trip

Stop at least every two hours at designated rest areas off the freeway to stretch and relax.

Allow plenty of time to drive carefully and within the law.

Because its mission is to help man in the acts of life, in acts where, in spite of everything, man is alone and forcibly individual, in birth, suffering and death, medicine should remain one of the redoubts* of an imperilled individualism. . . . And let medicine not forget that it should remain independent if it is not to degenerate and lose its efficacy as well as its authority.—Georges Duhamel (1884-)

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*See Test Your Word Score Page 1411.

Duty, then, is the sublimest word in our language. Do your duty in all things. You cannot do more. You should never wish to do less. — Robert E. Lee

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No political organization since the world began ever developed a great industry. Even waterworks and the post office were developed by risks and energies of individuals pooling their resources under private management.

— Nation's Business

A High Calling*

Every sane human being is agreed that this longdrawn fight for time, which we call Life, is one of the most important things in the world. It follows therefore that you, who control and oversee this fight, and you who will reinforce it, must be amongst the most important people in the world. Certainly the world will treat you on that basis. It has long ago decided that you have no working hours that anybody is bound to respect, and nothing but extreme bodily illness will excuse you in its eyes from refusing to help a man who thinks he may need your help at any hour of the day or night. Nobody will care whether you are in your bed or in your bath, on your holiday or at the theatre. If any one of the children of men has a pain or a hurt on him you will be summoned. And, as you know, what little vitality you may have accumulated in your leisure will be dragged out of you again.

In all times of flood, fire, famine, plague, pestilence, battle, murder, and sudden death, it will be required of you that you report for duty at once, go on duty at once, and remain on duty until your strength fails or your conscience relieves you, whichever may be the longer period.

You remain now perhaps the only class that dares to tell the world that we can get nothing more out of a machine than we put into it; that if the fathers have eaten forbidden fruit the children's teeth are liable to be affected. Your training shows you daily and directly that things are what they are, and that their consequences will be what they will be and that we deceive no one but ourselves when we pretend otherwise.

Have you ever considered what a tremendous privilege that is? At a time when few things are called by their right names, when it is against the spirit of the times even to hint that an act may entail consequences — you are going to join a profession in which you will be paid for telling men the truth, and every departure you make from the truth you will make as a concession to man's bodily weakness, and not his mental weakness.—Rudyard Kipling

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*Address to Students at the Middlesex Hospital, 1908.

WHAT'S YOUR DIAGNOSIS?

A 29-year-old housewife was admitted to the hospital for evaluation of easy fatigability, ill-defined abdominal pain, nausea, and aching pain in the back and legs, particularly the tibiae, of $2\frac{1}{2}$ years duration. She had been seen on several occasions during this period for more acute episodes of abdominal pain. Various diagnoses, such as acute appendicitis, peptic ulcer, and porphyria, were considered and discarded. Several L.E. cell preps were negative. There was no history of toxic or drug exposure.

On physical examination, several small posterior cervical lymph nodes were noted. The liver was enlarged 3 cm., and the spleen 2 cm., below the costal margins. There was slight fissuring around the mouth, and the hair was somewhat sparse around the anterior crown. Axillary and pubic hair were normal.

Routine blood counts, urinalysis, sedimentation rate, liver function tests, and sternal bone marrow were all normal. X-rays of the chest, upper GI, colon, and gallbladder were negative. Liver biopsy was being considered when further questioning into specific drug exposure led to the correct diagnosis.

What is your diagnosis? Turn to page 1386.

Iatrogenic Arterial Injuries*

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THE PHYSICIAN'S role in diagnosis and treatment of injury and disease states is clear; less well defined is his part in causation of disease. Many practitioners are involved in diagnostic and therapeutic techniques which carry potential for injury. They are aware of the risks entailed and zealously guard against complications. They recognize that when injury to the arterial system occurs, a critical need exists for repair of the induced abnormality. In short, immediate recognition of iatrogenic arterial injury allows rapid repair with restoration of vital blood flow.

The frequency of iatrogenic arterial injuries is increasing, but such trauma is at least as old as recorded medical history. In the first century Galen referred to aneuryms caused by blood letting.[1] Later, arteriovenous fistulas were well documented by William Hunter in 1764 and described as ". . . what is produced in the mouth by continuing the sound of the letter R in a whisper. It *(the bruit)* is strongest at the very place where the vein was punctured and became gradually less perceptible from that part upward."[2] The terms varicose aneurysm and aneurysmal varix were defined by Hunter and the pathologic anatomy of the fistulous arborization was described.

In classification of iatrogenic arterial damage, classical categories serve well. These are divided into injuries with acute or chronic manifestations. External hemorrhage, expanding hematomas, pulsating hematomas, and/or sudden distal ischemia characterize acute injury and demand immediate attention. Later, occult hemorrhage may resolve into a false aneurysm; or simultaneous arterial and venous injury may allow arterial blood to flow directly into a

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*Read before the Clinical Program on Trauma, Clinical Conference, Chicago Medical Society, March 2, 1966.

**From the Department of Surgery of the Northwestern University Medical School, 303 E. Chicago Avenue, Chicago, Illinois 60611.

Aided by the Northwestern University Vascular Research Fund.

vein. These two entities, false aneurysm and arteriovenous fistula, become late results of iatrogenic arterial injury if they are unrecognized and untreated in the acute stage.

Arterial Injuries Associated with Orthopedic Disorders

Some of the most interesting and dramatic manifestations of arterial injury accompany orthopedic disorders because of the peripheral nature of orthopedic surgery where large vascular channels lie adjacent to traumatized bone. Deep, relatively fixed vessels are vulnerable[3] to damage accompanying fractures or fracture treatment. Sometimes these injuries attend placement of the hardware of fixation. Bassett and Houck describe such an instance in which a false aneurysm of the deep femoral artery was caused by an overly long screw used to hold a femoral plate.[4]

Among orthopedic operations[5] there were 59 related to surgery of intervertebral discs, 51 accompanying excision of ganglion of the wrist, 32 occurring during arthrotomy of the knee, and 26 following triple arthrodesis of the ankle.

Intervertebral Disc Operations

The location and relative fixation of the aorta and the iliac veins make these vessels particularly liable to injury during removal of the L-4-5 lumbar disc. If disc degeneration involves the anterior wall, it may fail to offer a firm barrier to the exploring rongeur forceps. If the forceps are allowed to penetrate, tearing of the veins or arteries anterior to the spine may occur.[6] A mortality rate of 47 to 61 percent attends such a complication.[7,8]

If injury to a major artery occurs during disc surgery, bleeding may appear in the disc space. This is present in about one half of reported cases. Later, shock develops, due to retroperitoneal hemorrhage. This usually appears as the patient is turned from the prone to the supine position.[9] Heroic measures may be necessary to support life.

If the artery and vein are injured together during disc surgery, immediate hypotension may not be seen, since blood lost is quickly returned to the circulation. However, signs of distal venous hypertension, cardiomegaly, widening of pulse pressure, appearance of an abdominal systolic to-and-fro murmur

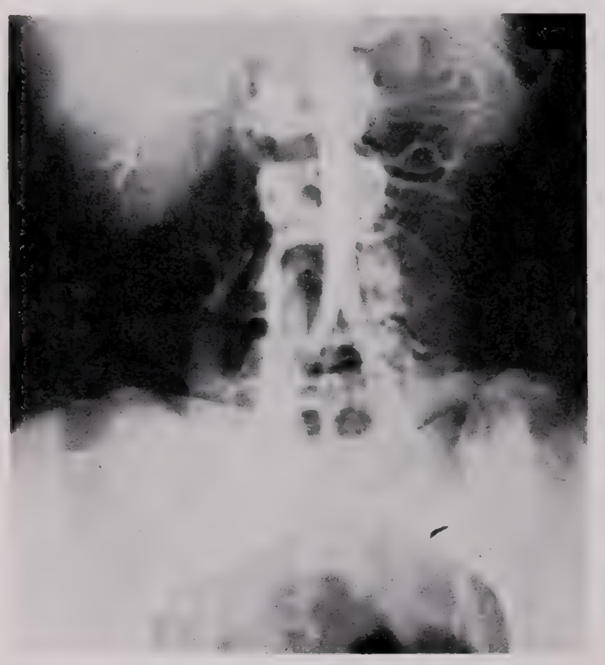

Fig. 1 — This aortogram, performed 19 years after appendectomy, shows an arteriovenous fistula between the ileocolic artery and the superior mesenteric vein. This portal system a-v fistula produced no cardiac abnormality.

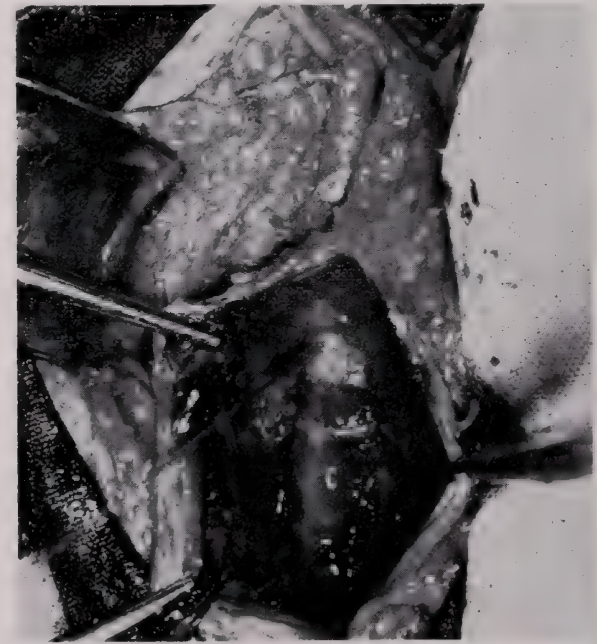

Fig. 2 — The false aneurysm caused by the arterial catheter has been opened. The femoral artery puncture site and its forceful jet of blood are well seen as the aneurysmal walls are retracted.

and eventual cardiac failure should lead to a rapid diagnosis of aorto-iliac arteriovenous fistulization.

Lateral Meniscus Operation

Other arterial injuries accompanying orthopedic operations include injuries to the lateral inferior genicular artery during removal of the lateral meniscus of the knee and arteriovenous fistula of the superior gluteal vessels caused by intramedullary femoral rodding.[10,11]

Excisional therapy in bone and joint surgery, much like major ablative procedures done elsewhere for malignancy, can cause arterial injury, as illustrated by the following case:

Case Report

Case No. 1

Biopsy of a recurrent giant cell tumor of the distal femur in a 48-year-old woman had shown this lesion to be benign. During excision of the large tumor, the popliteal artery was transected and repaired. Postoperatively the foot was pale, cold, pulseless, mottled and anesthetic despite administration of vasodilators and heparin. A secondary repair of the vessel was accomplished after excising the previously traumatized and sutured artery. Peripheral pulses, distal sensation and function were restored.

Determination of need for secondary arterial reconstruction was based upon recognition of traditional manifestations of ischemia, especially loss of epicritic sensation and motor function. Division of adjacent collateral vessels gave additional length to allow anastomosis without tension.[12]

Arterial Injury Associated With Abdominal Surgery

Since almost every operation can be associated with major arterial trauma, it is surprising that difficulties arise as seldom as they do.[13] Acute injury to vital arteries must be recognized and successfully treated immediately if life is to be preserved. Such instances arise when the hepatic or superior mesenteric artery is involved.

Case No. 2

During elective cholecystectomy, hepatic artery laceration was recognized. Hemorrhage was controlled by packing, and vascular consultation was obtained. Hemostasis was achieved by application of Potts vascular clamps. The hepatic artery was skeletonized,* the laceration was excised and the artery repaired with interrupted sutures. During an uneventful postoperative recovery, prophylactic antibiotics were administered.

Immediate recognition of the potentially fatal injury allowed rapid repair without observable hepatic ischemic damage.

Arterial Injury with Other Operations

Late manifestations of arterial injury can follow virtually every major operation. Late arteriovenous fistulas after thyroidectomy, mastectomy, splenectomy, nephrectomy, gastrectomy, hysterectomy and amputation are listed.[14] Chief offenders are operations in which a major vascular pedicle is ligated as a single unit. The mass ligature is a notorious producer of arteriovenous fistulas, as is the transfixion ligature. In the latter instance, the artery and vein are pierced simultaneously and arterial hemorrhage is decompressed into the venous circulation.

Case Report: A 34-year-old woman was found to have a loud machinery murmur over her entire abdomen. An appendectomy had been performed at age 15. No cardiac abnormality was present nor was hepatic dysfunction noted. An aortogram showed communication of the ileocolic artery and a branch of the mesenteric vein (Figure 1).

Arteriovenous fistulas involving the portal system are not common but can follow splenectomy or gastrectomy.[15,16,17] While these can produce portal hypertension and hepatic congestion, systemic cardiovascular responses are tempered by the liver acting as a circulatory buffer.

Arterial Injury Associated with Diagnostic Procedures

The most common type of iatrogenic arterial injury today follows diagnostic procedures which necessitate arterial puncture. Among these are cardiac catheterization, catheter angiography and direct arterial angiography. Complications following such investigations may be related to contrast media, premedication and even to the underlying disease process. These are not under consideration in this report.

In surveying 300 radiologists by questionnaire, Lang discovered 81 serious complications in 11,402 investigations utilizing the

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*See Test Your Word Score Page 1411.

Seldinger technique.[18] This certainly must represent the minimum risk of this type of manipulation. Lang found that minor complications of arterial spasm, local hematoma and vessel puncture were frequent (3%) but did not cause more than transient minor discomfort.

The most common single serious complication of arterial catheterization is thrombosis. This develops at the site of needle puncture, is associated with poor vascular status of the patient, long duration of the diagnostic procedure and inexperience of the investigator. Low output cardiac states contribute to frequency of post-catheterization thrombosis. Other complications also occur.

Case No. 3

This 60-year-old woman underwent a prolonged and difficult cardiac catheterization for diagnosis of aortic valvular insufficiency. Her blood pressure was 180/50. Twenty-four hours after the study a rapidly expanding pulsating hematoma of the groin developed at the site of one of the femoral artery punctures. This was repaired surgically.

Atherosclerosis, a pounding Corrigan pulse (water hammer type pulse), and prolonged arterial catheterization all combined to effect rupture of the femoral puncture site.

Case No. 4

Following uneventful cardiac catheterization, a groin hematoma persisted for three months in this 34-year-old male. Suddenly the character of the mass changed; it enlarged, became tender and caused a hip flexion contracture. At surgery the false aneurysm was opened and the puncture wound of the common femoral artery closed with a single suture (Figure 2). Subsequently this artery was used during cardiopulmonary bypass while the mitral valve was being replaced.

Despite an uncomplicated, brief arterial catheterization, performed by an experienced investigator, a false aneurysm developed. The case illustrates the inexorable progression of an aneurysm once it becomes established.

Other complications of retrograde arterial catheterization include dissecting aneurysm of vessels and subintimal, intramural arterial hematomas.[19,20] These combine to form the largest single category of arterial injury now seen by surgeons interested in vascular repair.

While catheter injuries of arteries are important, single needle punctures are also implicated in causation of arterial injury. Such injuries have followed thoracentesis, trigeminal nerve injections and even diagnostic venous puncture.[21] More rarely, an arteriovenous fistula has been encountered following vertebral arteriography.[22] This has not been seen by us following brachial retrograde angiography.[23]

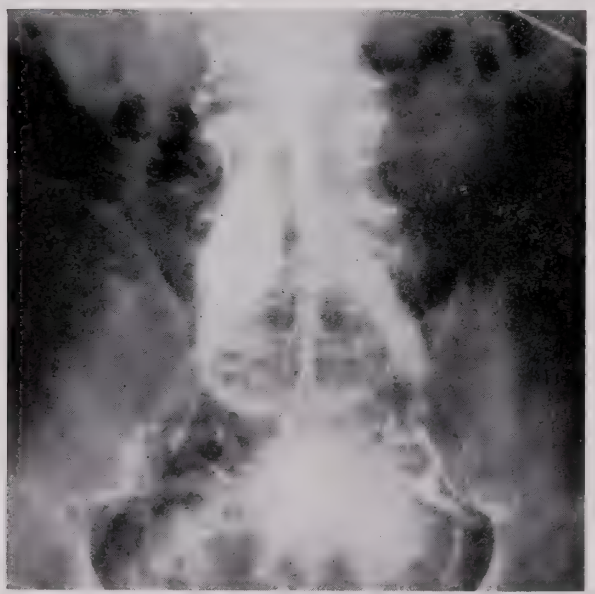

Fig. 3 — This aortogram shows a false aneurysm of the right iliac artery following a chronic disruption of an artery-graft suture line placed five years previously.

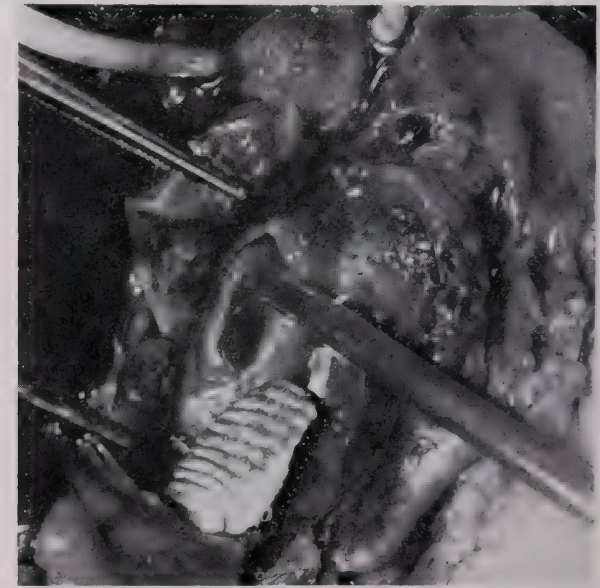

Fig. 4 — At surgery the graft is seen lying free within the false aneurysm. The disruption is attributed to failure of the silk suture and not to arterial degeneration.

Arterial Injury Associated With Vascular Surgery

In addition to technical problems of vascular reconstruction, the vascular surgeon encounters iatrogenic arterial injury as a result of graft infection with suture line disruption, autogenous venous patch blow-out and late failure of graft artery suture line.

Infection following graft implantation is a tragedy with horrible implications. Robert Shaw has said that if graft infection develops, one ". . . loses the patient or a large part of him." Principles of dealing with such problems include bypass of the infected graft and excision of the infected foreign body.

Less well known is the entity of central necrosis of an autogenous venous patch with massive postoperative hemorrhage.[24] In this complication the vein wall undergoes irreversible ischemic necrosis during implantation as an arterial patch. Blow-out of the central necrotic area occurs up to 48 hours after arterial reconstruction.

False aortic aneurysms adjacent to graft-artery suture lines are being seen by vascular surgeons with increasing frequency. These occur months or years after graft placement, behave exactly like true aortic aneurysms, and result from continued arterial degeneration, loss of suture strength, relative nonporosity or loss of strength of the graft material, such as nylon or orlon.[25]

Case No. 5

This 72-year-old man was found to have a pulsating lower abdominal mass five years after placement of an iliofemoral bypass graft. Aortography defined the lesion and surgical exploration revealed complete artery-graft suture-line disruption with false aneurysm formation (Figures 3 and 4).

A strong arterial wall and intact graft were found at re-exploration. The suture material used during graft implantation was silk. Apparent nonhealing of graft to artery occurred and, as the silk lost strength, the graft pulled away from the artery.

While continued arterial degenerative changes doubtless contribute to development of these post-reconstruction false aneurysms, the materials used in repair are also important. Recent development of dacron and polyethylene suture has allowed use of materials which do not lose tensile strength after implantation.

Conclusions

Physicians cause injury to arteries now just as they did in the time of Galen. Instruments and indications for violation of bodily integrity change, but the fact of arterial injury caused by the attending doctor remains. At this time the largest single category of arterial injuries caused by a physician follows arterial catheterization and is largely due to the increased use of this valuable diagnostic tool. Other causative factors include lack of experience of the physician performing the examination, technical difficulties of the procedure and long duration of the catheterization. It is to be expected that the incidence of this type of injury will decrease, but that the frequency of its occurrence will increase. This will be due to the value of catheter angiography in diagnosis and treatment of disease states and the increased use of the technique.

Just as the frequency of iatrogenic arterial injury can be expected to increase, the frequency of repair of such injury should increase. It is clear that major complications in the past have occurred in part because of delay in recognizing and effecting arterial repair. Since early repair is relatively easy before distal irreversible thrombosis occurs or exsanguinating hemorrhage develops, it is to be expected that restoration of arterial integrity will be the standard of acceptable therapy for this condition in the future.

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'Tis but a base ignoble mind, that mounts no higher than a bird can soar.
— Shakespeare

Photographic Contest

The Editors of MINNESOTA MEDICINE, in collaboration with the Doctors' Photographic Society of Minneapolis, take pleasure in announcing a monthly photographic contest. The contest is to promote an interest in photography in the medical profession. First prize each month will be publication in full color of the winning picture in MINNESOTA MEDICINE.

The following rules will govern the conduct of the contest:

1. Only doctors of medicine are eligible to submit pictures, and the picture must have been taken or composed by a physician.
2. Each contestant may submit not more than two pictures each month.
3. Only color transparencies, 35 mm. to 2¼", can be considered.
4. Each slide should be labeled with the maker's name, address, and the identifying title.
5. Slides should not be mounted on glass, but can be protected in plastic sleeves or envelopes.
6. Each entry must be accompanied by a self-addressed, stamped envelope if return of the picture is desired. Returns will be made shortly after the close of the contest each month. The winning photograph will be retained but will be returned after it has been used.
7. The deadline date for entry will be the 10th of each month and the winner of each month's contest will be announced in MINNESOTA MEDICINE in the subsequent issue. The date of publication will be three to six months in advance.
8. There will be no limitation on subject material except as indicated in item 10.
9. Model releases will be requested of winners where appropriate.
10. Judges will be selected by the editors of MINNESOTA MEDICINE and the Doctors' Photographic Society. The judges will be guided by the precepts of the Photographic Society of America, and winners will be based on appropriateness, interest, impact, and technical excellence.
11. The editors of MINNESOTA MEDICINE and the Doctors' Photographic Society cannot be responsible for entries lost or damaged, but every effort will be made to protect submitted pictures.

Your pictures are hereby invited. Please submit pictures to:

Photo Contest Editor
MINNESOTA MEDICINE

Voided Urine Cultures in Women

A Study of 425

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In recent years the value of urine cultures obtained by catheterization and planted on broth cultures or other non-quantitative means has been rightfully questioned.[1-5] Observations that the urethra is not sterile as was once assumed lend credence to the idea that bacterial growth per se on cultures of voided urine need not be indicative of urinary infections.[6-9] It also follows that passage of a catheter through a contaminated urethra may result in a growth of bacteria in the culture medium which is not indicative of a urinary tract infection. Furthermore, thrusting a catheter through the bacterial flora in the urethra may introduce these bacteria into the bladder. It is estimated that a clinical urinary tract infection results from a single catheterization in two to four percent.[10,13]

Marple[11] in 1950 made use of a colony count method in quantitating bacteriuria, but the method did not come into widespread use until recent years. Many studies have now been carried out which indicate the value of a quantitative estimate of bacteria in urine cultures as a means of differentiating contaminants from the bacteria involved in an active urinary infection.[1,2,3,10,12] What is found in a urine culture is not so important as how many bacteria appear in the culture. It has long been acknowledged that clean, voided specimens in males are associated with a minimum amount of contamination, but there has been some reluctance to accept the idea that voided urine cultures in women are equally uncontaminated.

A growing number of studies have indicated, however, that clean voided urine cultures are quite valid in women.[13-16] Since catheterization of female children may be very traumatic, psychologically if not physically, application of this method to children would be welcome.[17]

There seems to be unanimity of opinion

that less than 1,000 bacteria per cc. of urine are indicative of contamination, and greater than 100,000 bacteria per cc. as pathognomonic of urinary tract infection. There is no agreement on the significance of counts between 1,000 and 100,000. Some feel that counts above 10,000 are significant; others place their significant count much higher.

The first purpose of this study was to try to ascertain whether or not voided urine cultures would be clinically useful. The second purpose was to determine what numbers of bacteria would be considered normal and abnormal by our method. The patients in the study were all women in a general hospital,* their ages ranging from one to ninety-one years.

The cooperation of the medical staff was obtained in order to get a large number of voided cultures in women who were clinically free of urinary tract infections. Voided cultures were also obtained from patients who had clinical urinary tract infections. The results of all the voided urine cultures obtained from women during the period of the study, covering the approximately two-year period from 1959 to 1962, were recorded in the laboratory. The author then reviewed the charts of all the patients involved and categorized the patients according to whether clinical urinary tract infections did or did not exist, based on the evidence on the chart. Aside from the effort to obtain a large number of clinically infection-free patients, there was no attempt made to select the patients. All female patients with voided urine cultures during this period of time are included in the study. There were 308 cases considered to be clinically free from urinary tract infections and 117 cases with a diagnosis of urinary tract infections. Cystitis was the most common diagnosis. There were also a number of cases of pyelonephritis. In an additional 21 cases there was insufficient data on the chart to permit categorization with reasonable assurance, or the clinical diagnosis or absence of diagnosis in the author's opinion conflicted with the data in the chart.

Method

The patients are instructed to cleanse the external genitalia thoroughly with Phisoderm. Some authors have described rather elaborate cleansing and disinfecting regimens.[16,18] However, we have not used antiseptics or antiseptic soaps, as we believe that the use of antiseptics will not add materially to a thorough cleansing and rinsing. The patient is next instructed to void the initial urine into a urinal and then to discard it. The last part of the urine is then voided into a sterile, large-mouthed jar. This urine is immediately sent to the laboratory and cultured within fifteen minutes. Since urine itself is a good culture medium, a spuriously high count may be obtained in a urine which is allowed to stand before culturing.

The Culture Media

In the laboratory the freshly collected urine cultures were innoculated on appropriate media as soon as they were received. In general, two types of media were used. One plate consisted of a selective medium for the isolation and preliminary identification of gram-negative rods. The selective plates used were Tertigol-7 Agar, Eosin Methylene Blue Agar or Desoxycholate Agar. Urine was also innoculated on a blood agar plate containing either sodium azide or phenyl ethyl alcohol to inhibit gram-negative rods.

The Method of Counting

During the initial part of the study colony counts were performed by making a 1:10 dilution of urine in saline and innoculating 0.1 cc. on the surface of the appropriate plates and spreading the urine evenly over the plate surface with a bent glass rod. Later in the study the innoculation of the plates was made with undiluted urine, using a calibrated platinum loop having a 4 mm. inside diameter capable of delivering 0.01 ml. of urine. The urine was spread evenly over the surface of the plates. Colony counts of gram-negative and gram-positive cocci were made from the appropriate plates at the end of twenty-four hours. Further isolation and identification of the gram-negative rods were made by the usual biochemical techniques. Identification of enterococci was made by innoculation of suspected colonies into a fluid medium containing dextrose, sodium azide and Brom Cresol Purple (SF Medium, Baltimore Biologic Laboratories). Staphylococci were identified on the basis of pigment production, hemolysis and coagulase reaction.

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Results

The Clinically Uninfected Group

The results of the cultures in the 308 females deemed to be clinically free from urinary tract infections are shown in Tables 1 and 2. The organisms shown in Tables 1 are all other than Staphylococci. It may be seen that 87% of these urines had colony counts of 0-1000 per cc., and 97% had colony counts of 0-5,000 per cc. Counts of 0-10,000 per cc. appeared in 99% of these cases. There were two cases where the counts ranged from 10,000 to 20,000 and one case with a pure culture of 30,000 E. Coli per cc. Of course one may question whether this latter case might not, in fact, represent a sub-clinical urinary tract infection; but there was no definite evidence to support this.

Staphylococci were cultured in 93 instances. It should be noted that these cultures and 234 non-Staphylococci cultures add up to more than 308 total cultures since in some instances more than one organism was cultured from a given urine. The colony counts of the cultured Staphylococci are shown in Table 2. It may be seen that 50% had counts of 0-1,000 per cc.; 72% had counts of 0-5,000 per cc.; 80% had counts of 0-10,000 per cc. In 98% the counts were 50,000 or less. In one instance there were 100,000 coagulase negative Staphylococcus albus per cc., and in another, 150,000 Staphylococcus aureus.

The types of organisms cultured and their relative frequency in the 308 clinically uninfected cases are shown in Table 3.

TABLE 1
234 Clinically Normal Cases
Organisms Cultured Other Than Staphylococcus

Colony Chart	Number of Cases
No Growth (Less Than 100)	131
100-500	53
501-1000	19
1001-1500	10
1501-2000	7
2001-5000	6
5001-10,000	5
10,001-20,000	2
20,001-30,000	1
	234

TABLE 2
93 Clinically Normal Cases
Staphylococcus Cultured

Colony Count	Number of Cases
1-500	24
501-1000	22
1001-1500	4
1501-2000	5
2001-5000	12
5001-10,000	7
10,001-20,000	9
20,001-30,000	2
30,001-50,000	6
50,001-100,000	1
Over 100,000	1
	93

TABLE 3
Organisms Cultured in Group of 308 Cases
Without Urinary Infection

Organism	Number of Cases Where Found	
Staphylococcus Albus	84	37%
Coliform Groups	73	32%
Proteus	24	10%
Enterococcus	17	8%
Staphylococcus Aureus	16	7%
Candida	5	
Diphtheroids	3	
Pseudomonas	1	
Non-Hemolytic Streptococcus	1	
Lactobacillus	1	

TABLE 4
125 Clinically Abnormal Cases With Urinary Tract Infection

Colony Count	Number of Cases
1-10,000	3
10,001-25,000	3
25,001-50,000	3
50,001-75,000	4
75,001-100,000	20
> 100,000	92

The Clinically Infected

Table 4 shows the colony counts obtained in 125 cases deemed to have clinical urinary tract infections, most of which were diagnosed as cystitis. There were some cases of pyelonephritis. In eight cases two organisms were considered to be etiological in the same clinical infection. It is seen that 74% of the cultured bacteria had colony counts greater than 100,000 bacteria per cc. Ninety percent of these cultures yielded greater than 75,000 per cc.; 93% had counts greater than 50,000 per cc.; 98% had counts greater than 10,000 per cc. Table 5 lists all of the organisms encountered in these cases with their frequency of occurrence. In only one of the cases with Staphylococci cultured was this organism felt to be etiological. In this case a coagulase positive Staphylococcus aureus was isolated in pure culture with a colony count of 100,000 per cc. In some cases organisms such as Enterococci, Coliform and Proteus were encountered in low counts of 10,000 or less along with organisms in larger numbers which were considered to be the etiologic agent of infection. This, of course, is the advantage of colony counts as they more positively identify the significant bacteria. In two cases additional organisms, E. Coli and Proteus, were found in larger numbers, the count being 45,000 per cc. in both cases. The significance of these organisms in the infective process is uncertain. In eight cases two organisms were considered to be etiological. All of the bacterial counts in these cases were 100,000 per cc. or over, except in one case where 90,000 Proteus per cc. were cultured. It should be noted that for the sake of simplicity, the Coliform group includes all bacteria identified as E. Coli., Paracolon, Klebsiella, Aerobactor and E. Freundia. Similarly the Pseudomonas group includes bacteria identified as Pseudomonas and Alkaligenes. Table 6 lists the organisms which were considered to be offending agents along with their frequency of occurrence.

TABLE 5
Organisms Encountered in 117 Urinary Tract Infection Cases (144 Organisms)

	Number of Cases Where Found	%
*Coliform Group	93	65
Proteus	21	14
Enterococcus	16	11
**Staphylococcus Albus	8	6
†Pseudomonas	3	2
‡Staphylococus Aureus	2	
Alpha Streptococcus	1	

*Includes E. Coli, Paracolon, Klebsiella, Aerobacter, E. Freundia.

**All of these were found with other organisms. In none was Staphylococcus Albus considered etiological.

†Includes Pseudomonas and Alkaligenes.

‡In only one was the Staphylococcus considered etiological (pure culture 100,000/cc).

TABLE 6
Organisms Considered Etiological Agents in 117 Urinary Tract Infections*

Coliform	90	72%
Proteus	18	14
Enterococcus	12	10
Pseudomonas	3	2
Staphylococcus Aureus	1	1
Alpha Streptococcus	1	1

*In 8 cases more than one organism was felt to be etiological.

There were three cases with counts of less than 10,000 organisms per cc. in the group of patients who had a clinical diagnosis of urinary tract infection. One case was diagnosed as hemorrhagic cystitis. Klebsiella, 7,500 per cc., were cultured from this urine. The other two cases were diagnosed as "chronic urinary tract infection." Both had had frequent instrumentation and treatment previously. One culture yielded Pseudomonas 1,200 per cc. and the other had Proteus 2,600 and E. Coli 2,400 per cc. It seems quite possible that the infection may have been in a relatively quiet phase in both of these cases at the time the culture was taken.

Discussion

From the data accumulated there seems to be reasonable evidence that this method of culturing urine can be reliably used in females. The ease by which urine collections can be made certainly has much to recommend it from the point of view of the nursing service and the patient. There is no danger to the patient from the urine collection, and follow-up cultures may be taken as necessary with no concern about ill effects. A very little more work is required from the laboratory; but this seems amply justified from the results obtained. The method is not so complicated that it cannot be used in any office or hospital with facilities for doing simple bacteriology. The infecting organisms may be more reliably determined and therapy therefore more accurate. There seems to be a wide separation between normal and abnormal numbers of bacteria which may be encountered in the urine, so that most of the time the results can be directly interpreted. Figure 1 shows a graphic representation of all the data obtained in this study from the cases both with and without clinical urinary tract infections. We believe that despite the fact that large numbers of Staphylococci may be cultured from the urine, clinical infection with this organism is rare. There was only one case in this series which was considered to be due to Staphylococcus.

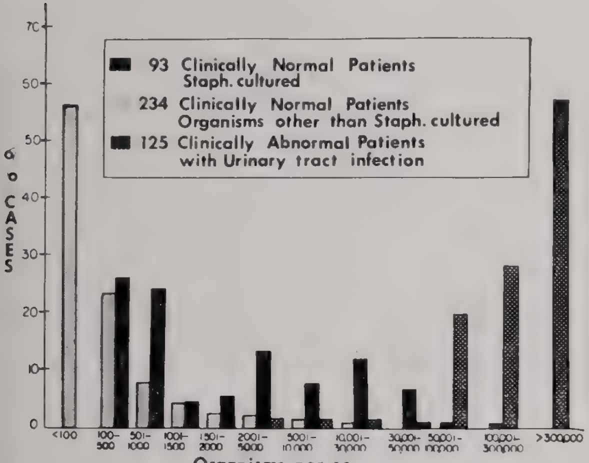

Figure 1

Conclusions

From the data it seems fair to say that a colony count of 10,000 or less in women may be regarded as normal with few exceptions. Counts of 1,000 or less are probably never associated with infection. A rapid urine flow with resultant dilute urine may lower the count. The urine should be in the bladder long enough for bacteria to multiply. A very acid urine pH may inhibit bacterial multiplication. An obstructed ureter may not allow the infecting bacteria to enter the bladder. Certain fastidious organisms (Group A Streptococci, some Streptococcus viridans, occasional Staphylococci or Enterococci) may grow poorly in urine. A bacteriostatic agent in the urine will lower the bacterial count.

On the other hand, colony counts of over 100,000 per cc. (Staphylococci excepted) seem invariably to indicate urinary tract infections, as noted by previous investigators. From the data presented here it would seem reasonable to accept counts of greater than 75,000 per cc. as definitely positive. Colony counts of 50,000 to 75,000 per cc. are probably significant. Counts of between 10,000 and 50,000 represent a grey zone. Most of these will probably be associated with urinary tract infection. A few counts in this range, however, may be normal. As in most laboratory tests, a generous pinch of medical acumen must be added. In the final analysis clinical judgment will prevail.

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10-30 May be secured from the author or the reprints.

Man's evolution to an upright position should be viewed in proper perspective. It took a billion years to develop low back pain. — Changing Times

Clinical Notes from Hippocrates' "Epidemics"

Case II: Silenus lived on the Broadway near the premises of Eualcidas. In consequence of exertion, drinking, and unseasonable exercises, he was seized with fever. Pain began in the loins.* Feeling of weight in head, and stiffness of neck. On first day discharge from bowel was bilious, unmixed, frothy, high-coloured, and abundant. Urine dark, with dark sediment. Thirst, dry tongue. No sleep at night.

Second day. Acute fever, stools more abundant, thinner and frothy; urine dark; bad night; slight delirium.

Third day. All symptoms exaggerated. In abdomen on both sides an oblong area of tension without anything solid below it, and reaching to navel. Stools thin, darkish. Urine turbid, darkish. No sleep at night; much talking, laughing, singing; unable to check himself.

Fourth day. Same.

Fifth day. Stools unmixed, bilious, smooth, fatty; urine thin, transparent; mind occasionally clear.

Sixth day. Sweated a little about the head; extremities cold and livid; much restlessness, no passage from bowels; urine suppressed; acute fever.

Seventh day. Speechless; extremities could not be warmed up; no urine passed.

Eighth day. Cold sweat all over; and with it red spots (exanthemata), round, small, like acne, persisted without subsiding. From bowels after slight stimulus abundant, thin, and as it were unconcocted matter was passed, with pain. Urine irritating and passed with pain. Extremities showed little warmth. Scanty sleep; tendency to coma; speechless; urine thin and transparent.

Ninth day. Same as before.

Tenth day. Drank nothing; comatose; scanty sleep. Discharges from bowel as before; urine thickish, coming away in bulk; on standing, left a white deposit, like meal. Extremities again cold.

Eleventh day. Death.

In this case, from the beginning and throughout, the breathing was deep and infrequent. Constant throbbing in abdomen. Age about twenty.

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*See Test Your Word Score Page 1411.

ANSWER TO WHAT'S YOUR DIAGNOSIS

(From page 1374)

Chronic Vitamin A intoxication. The patient had been taking between 50,000 and 100,000 units of Vitamin A for 4 or 5 years, originally prescribed for acne. Following this disclosure, her serum Vitamin A level was found to be 270 I.U. (normal less than 200). Definite symptomatic improvement occurred within a week after withdrawal of this medication. It is of interest that he patient did not think of Vitamin A as a drug, and hence did not mention it when asked originally about medications.

Early Ambulation

Long ago I learned from my father to put old people to bed only for as short a time as was absolutely necessary, for they were like a foundered horse; if they got down it was difficult for them to get up, and their strength ebbed away very rapidly while in bed. — Charles Mayo

Congenital Nonspherocytic Hemolytic Disease

With Erythrocyte Glucose-6-Phosphate Dehydrogenase Deficiency

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A DEFICIENCY OF the enzyme glucose-6-phosphate dehydrogenase in the red cell has been well recognized as the underlying abnormality responsible for hemolytic episodes in a substantial group of patients when exposed to a variety of drugs.[1-5] Originally described as a problem of "primaquine** sensitivity," it was found that in addition to antimalarial drugs, agents as diverse as the fava bean, chloramphenicol, and aspirin could precipitate an attack of hemolysis in these patients. The attacks are readily reversible if the inciting agent is discontinued and are self-limited when it is continued without an increase in dosage.[1,3-6] Even when these patients are not exposed to such an agent, a significant proportion have been found to have a red cell life span about 25 per cent less than normal and a reduced osmotic fragility, although they are usually not anemic.[1,7,21]

In contrast to this comparatively common disorder, more recently a complete or almost complete absence of this enzyme in the red blood cells has been described[8-21] in another group of patients. Characteristically chronic hemolysis is present in this group with severe exacerbations of hemolysis or episodes of bone marrow erythropoietic arrest following febrile illnesses. The exact relationship between this enzyme-deficiency, congenital nonspherocytic hemolytic disease and the primaquine-sensitive variety has not been clearly established. This report describes a typical case of the congenital nonspherocytic hemolytic type with post-splenectomy thrombotic complications which had not been observed previously in this condition.

Methods

Routine clinical tests were carried out according to standard laboratory techniques.

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**See Test Your Word Score Page 1411.

Special laboratory investigations included the autohemolysis test,[22] the Heinz body test,[23] determination of the reduced glutathione and the glutathione stability test,[24] measurement of erythrocyte glucose-6-phosphate dehydrogenase,[25] acid phosphomonoesterase,[26] and pyruvate kinase.[27]

Case Report

A 33-year-old white male of German ancestry was admitted to the Minneapolis Veterans Hospital for the first time in August 1963 for treatment of a residual, superficial thrombophlebitis.

Childhood History

At the age of three, following an upper respiratory infection, the patient was found to be "severely jaundiced and anemic." He was hospitalized and recovered uneventfully without blood transfusion. Despite the usual childhood diseases, the patient had no similar attack until he was fourteen years old. Then, in November 1944, over the course of a few days, he suffered profound fatigue, cough, nausea, chills and fever, while becoming progressively more pale and yellow. No history of prior drug or toxic exposure was elicited.

Childhood Physical Findings

He was referred to the University of Minnesota Hospitals where he was found to be an acutely ill child, restless, disoriented, with a temperature of 102° F. and a pulse of 160/min. Pertinent physical findings were marked pallor, icterus, and two-fingerbreadths hepatosplenomegaly.

Initial Laboratory Findings

Admission laboratory data included a hemoglobin of 2.1 g/100 ml., a wbc. of 9,250/mm^3, a platelet count of 380,000/mm^3, a reticulocyte count of 0.7%, and an icterus index of 12. Marked anisocytosis was observed in the peripheral blood smear, but there was no mention of spherocytes then or at any later time. The patient was transfused with 1300 ml. of whole blood over the next several days, with a prompt reversal of the bone-marrow arrest, as reflected in a reticulocytosis of 15% on the fifth hospital day, followed by an increase in the hemoglobin to 10.6 g/100 ml. Two fecal urobilinogen determinations on specimens collected during the transfusions were 2,960 and 3,360 Ehrlich units/100 g. Osmotic fragility was normal at this time. The diagnosis of a familial hemolytic anemia was made, and the patient advised to have an elective splenectomy after he had completely recovered from the attack.

Progress

In March 1945 the patient was readmitted and a 502-gram histologically normal spleen was removed. Preoperatively the platelet counts ranged between 280,000/mm^3 and 450,000/mm^3. In the immediate postoperative period the platelet count rose to 850,000/mm^3 but then promptly returned to the 450,000/mm^3 range.

For the next fourteen years the patient was asymptomatic, serving a two-year term in the Marine Corps during the Korean conflict without undue hardship. During this period his friends occasionally commented that his eyes were yellow at times when he felt unusually fatigued or suffered from an upper respiratory infection, but these episodes were never serious enough to warrant a physician's attention. In 1959, at the age of 28, the patient developed deep thrombophlebitis of the left calf for which he was hospitalized and treated with heparin. Evidence of the disease cleared rapidly, but in 1961 he developed a similar process in the right calf, and again there was a good response to heparin. In June 1963 the patient developed bilateral thrombophlebitis of the great saphenous veins. With heparin and oral anticoagulants there was considerable improvement except for residual pain in the inner aspects of his thighs. There was no history suggestive of pulmonary embolization during any of these episodes, nor was the patient aware of cyanosis or unusually severe shortness of breath.

Family History

The patient's father had died at age 39 from what was thought to be an "infection of the heart" and his mother at age 44 from a malignancy of unknown type. One sister is well and free of jaundice or anemia. All five of the patient's children were jaundiced at birth, but this condition was very transient and they have developed uneventfully since.

Adult Physical Findings

On physical examination the patient was afebrile with a blood pressure of 130/80 mm Hg. The pulse was 84/min. with many premature beats. He was a well-developed, cooperative young man in no distress. There was no apparent jaundice. The heart was normal in size with an accentuated second pulmonic sound, a right ventricular heave and a pulmonic ejection click. Examination of the abdomen revealed a well-healed left upper quadrant scar and no hepatomegaly. All peripheral pulses were present but substantially reduced. A small, chronic ulcer of the left calf was evident and both greater saphenous veins in the thighs were firmly thrombosed and surrounded by relatively mild inflammatory reactions. There was no evidence of deep vein phlebitis.

Laboratory Studies

Initially the hemoglobin was 15.8 g/100 ml., the leukocyte count 11,850/mm^3, the platelet count 406,000/mm^3 and the reticulocyte count 8.8%. The red blood cell indices were normal (MCH. 33 $\mu\mu$g, MCV. 99 μ^3, MCHC. 34%), and on peripheral smear stipled red cells and Jolly bodies were seen. A random stool sample contained 1,252 Ehrlich units of fecal urobilinogen/100 g. Total serum bilirubin was 2.8 mg/100 ml. with a direct fraction of 0.5 mg/100 ml. The red cell fragility was normal. Bleeding and clotting times, hemoglobin electrophoresis, fetal hemoglobin, plasma hemoglobin, blood urea nitrogen, two-hour post-prandial blood sugar, serum cholesterol, serum glutamic oxalecetic transaminase, serum electrophoresis, prothrombin time, cephalin cholesterol flocculation test, protein-bound iodine, and serum vitamin B$_{12}$ were all within normal limits.

Lupus erythematosus cell preparation, the acid hemolysis test, the direct and indirect Coomb's test, tests for sickle hemoglobin, cryoglobulin, cold agglutinin and serologic test for syphilis were all negative. Stool guaiacs were consistently negative.

Chest x-ray (Figure 1) demonstrated markedly increased central pulmonary vascular markings and decreased peripheral markings. Cardiac cinefluoroscopy confirmed the prominence of the main pulmonary artery as well as the right ventricle, both with increased pulsations. The radiographic picture was not considered compatible with an intracardiac shunt.

Electrocardiogram showed right axis deviation, right ventricular strain, and multiple premature ventricular contractions, the entire pattern being compatible with pulmonary hypertension. Normal mechanics and lung volumes were demonstrated on pulmonary function tests. An oral cholecystogram was normal. Half-life survival of autotransfused Cr^{51}-labeled red cells was only 7.5 days in contrast to the normal half-life of 39 days of tagged normal donor cells.

A bone-marrow aspirate showed increased iron stores, increased siderocytes, and normoblastic hyperplasia. Oscillometric studies revealed markedly reduced peripheral pulsations in all extremities.

The autohemolysis test demonstrated 9.6 to 12.4 per cent spontaneous hemolysis after 48 hours incubation on three different occasions (normal 1.0-3.5). With the addition of glucose the corresponding values ranged from 5.2 to 6.5 (normal range 0.0-0.7). The Heinz body test showed that 73 per cent of the erythrocytes contained five or more inclusion bodies (normal range 0-4). The value for reduced glutathione was 44 mg/100 ml. RBC. (normal range 53-79) and for the glutathione stability test 7.5 mg/100 ml. RBC. (normal range 46-71). The concentration of glucose-6-phosphate dehydrogenase in the erythrocytes was zero (normal range 6.0-8.7 U/100 ml. RBC.) while that of pyruvate kinase was 4.93 U/100 ml. RBC. (normal range 2.0-3.4) and that of acid phosphomonoesterase was 36.2 units (normal range 8.9-35.4).

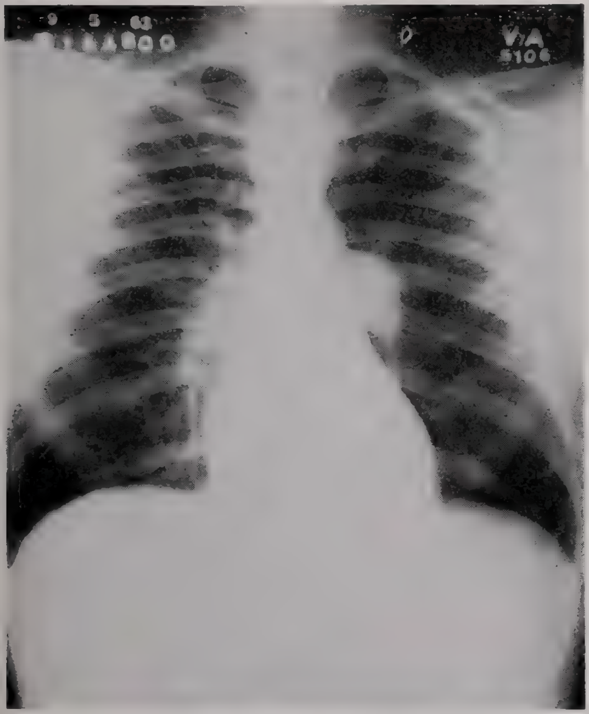

Fig. 1 — PA chest film. Prominent pulmonary artery and main pulmonary artery branches with anemic peripheral vascular markings compatible with pulmonary hypertension.

Treatment and Progress

With bed rest, hot packs, a short course of phenylbutazone, and warfarin sodium there was a rapid and complete clinical clearing of the bilateral superficial phlebitis. Since the persistently high platelet level ($400,000/mm^3$-$900,000/mm^3$) most likely predisposed him to deep vein phlebitis from which he had shed multiple subclinical pulmonary emboli with resultant pulmonary hypertension, it was decided to reduce the platelet count with busulfan. Although it was possible to lower the platelet level to a minimum of $243,000/mm^3$, this was accomplished only at the expense of suppressing the patient's increased hematopoietic activity until the hemoglobin fell to 11.9 g/100 ml. and the wbc. to $3,200/mm^3$; so the drug was discontinued. The patient was discharged on long-term warfarin sodium therapy alone.

Two weeks later he was readmitted. Having forgotten to take his daily dose of warfarin sodium once, the patient took a double dose on the next day. On the following day, while deer hunting, he slipped and fell on his right arm and right flank. Subsequently, until his admission about twenty-four hours later, he developed gradually increasing pain in the right flank radiating into the right groin with darkening of the color of his urine.

Pertinent physical findings on admission included marked right costovertebral angle tenderness without palpable masses. Urinalysis revealed a full field of red cells, but no clots were passed. Prothrombin time on admission was 44 seconds with a control of 12 seconds. His initial hemoglobin was 12.6 g/100 ml., the wbc. $7,550/mm^3$, the platelet count $429,000/mm^3$ and the reticulocyte count 10.6%. An intravenous pyelogram was unremarkable. Treatment consisted of analgesics, cessation of the warfarin sodium and small doses of parenteral vitamin K. On these measures the prothrombin time promptly returned to the normal range and all signs and symptoms of what was considered to be a small renal or perirenal hematoma subsided. Concomitant with this course, however, over a period of five days the patient developed three definite areas of new superficial phlebitis of the lower extremities. Hot packs, phenylbutazone, and intravenous heparin were employed. With clearing of the phlebitis the patient was again discharged on long-term warfarin sodium therapy.

Discussion

Clinical Features

The patient in this report manifests a congenital nonspherocytic hemolytic disease characterized by chronic increased hemolytic activity that was always well-compensated except after two relatively mild febrile illnesses. On at least one of these occasions he apparently experienced a selective bone-marrow arrest of erythropoiesis with severe anemia. Anemia then, though an important part of this disease, is not an invariable one; in many of the cases it is present only intermittently, and was never documented at all in seven of the twenty-seven cases in which it was clarified in the literature (Table 1). As indicated by his history of "yellow eyes" and fatigue periodically through the years, probably the patient reported here suffered many episodes of increased hemolytic activity with jaundice. Jaundice was present in all but two of the twenty-eight cases at some time in their course (Table 1).

On the other hand, it is apparent that many substantial illnesses, for instance all of the childhood exanthemata to which this patient was subject, do not produce significant hemolysis or bone-marrow arrest. It is undoubtedly for this reason that the diagnosis of congenital nonspherocytic hemolytic disease is not one that will be made exclusively in childhood. Of the twenty-six cases in the literature in which the age is given, twelve were diagnosed after the age of thirty (Table 1). The oldest patient in this series, a 59-year-old man, although found to be mildly icteric or anemic on several occasions through the years, apparently required transfusions only once.[20] Splenomegaly was present at some time in thirteen of twenty-three cases where it was described, but only three patients including the present one have had splenectomies (Table 1).

Laboratory Characteristics

The osmotic fragility test was normal and the Cr^{51} red cell half-life substantially reduced in our patient, as was the case in all reports in the literature in which these were elucidated (except for three mild increases in the osmotic fragilities) (Table 1). The enzyme analyses in the patient studied in this report failed to detect any glucose-6-phosphate dehydrogenase, whereas the pyruvate kinase concentration was slightly increased, probably due to the high reticulocyte count. Glutathione was low, the glutathione stability test was abnormal and the Heinz body test was strongly positive. These findings are typical of glucose-6-phosphate dehydrogenase deficiency congenital nonspherocytic hemolytic disease.

Sex-Linked

Since the vast majority of cases of this disease have occurred in males, there can be little question that this is a sex-linked abnormality. A highly variable expressivity in the female heterozygous for this condition has been shown,[14,18-20] some manifesting normal enzyme levels, some borderline low and some markedly deficient values, the latter with mild anemias and increased reticulocyte counts. The three daughters of the patient presented here all had enzyme values well within the normal range, as did his two sons and four of his first cousins. Utilizing the same method, it was not possible to demonstrate any glucose-6-phosphate dehydrogenase activity in the patient's erythrocytes.

Defects in Glycolytic Pathways

It is generally believed that defects in the glycolytic pathway are the cause for the hemolysis in patients with this disease. So far deficiency has been found in glucose-6-phosphate dehydrogenase,[8-21] pyruvate kinase,[28-31] reduced glutathione,[32] glutathione reductase,[33] diphosphoglyceromutase[34] and glyceraldehyde phosphate dehydrogenase.[35] It is only reasonable to believe that there are still others. The first attempt at more detailed studies of these anemias was made by Selwyn and Dacie.[22] Using the autohemolysis test, these workers divided the congenital nonspherocytic hemolytic anemias into two distinct types. Type I showed no or only a moderately increased autohemolysis at 48 hours, with a minor improvement with the addition of glucose. Type II showed a great increase in autohemolysis at 48 hours with no improvement, or even further hemolysis with the addition of glucose.

The patient presented in this report and all six of the other cases of glucose-6-phosphate dehydrogenase deficiency congenital nonspherocytic hemolytic disease on whom the test was performed clearly fit into the Type I of Selwyn and Dacie. It is generally believed that Type I represents glucose-6-phosphate dehydrogenase deficiency and Type II the pyruvate kinase deficiency. Oski

TABLE I
Clinical and Laboratory Characteristics of Congenital Nonspherocytic Hemolytic Anemia With Erythrocyte Glucose-6-Phosphate Dehydrogenase Deficiency

Author	Background		Age at Dx & Study	Onset of Jaundice or Anemia (in yrs.)	Jaundice Ever	Anemia Ever	Splenomegaly Ever	Splenectomy	Osmotic Fragility	Cr^{51} T/2	Auto Hemolysis Saline/Glucose 48 hr.	48 hr.
Kirkman[8,9]	No. Cen. Europe	(1)	16	7	Yes	Yes	Yes					
Kirkman[8,9]	No. Cen. Europe	(2)	39	12	Yes	No	Yes					
Kirkman[8,9]	No. Cen. Europe	(3)	50	2/12	Yes	Yes	Yes	Yes (833 g)				
Kirkman[8,9]	No. Cen. Europe	(4)	30	Neonate	Yes	No	Yes					
Kirkman[8,9]	S. Europe	(5)	1 4/12	3/12	Yes	No	No					
Kirkman[8,9]	No. Cen. Europe	(6)	3 C	Neonate	Yes	Yes	Yes	Yes	Sl↑ N			
Kirkman[8,9]	No. Cen. Europe	(7)	5 C	1 7/12	Yes	Yes	Yes		N			
Waller[10,11]	Iranian	(8)	30	23	Yes	No	No		Sl↑			
Waller[10,11]	Iranian	(9)	41		No	No	No			5 days		
Newton[12,13]	S. Europe	(10)	4	Neonate	Yes	Yes						
Newton[12,13]	?	(11)	?	Neonate	Yes	Yes						
Newton[12,13]	?	(12)	?	Neonate	Yes	Yes						
Zinkham[14,15]	No. Europe	(13)	6 B	2	Yes	Yes	No		N			
Zinkham[14,15]	No. Europe	(14)	2½ B	1	No	Yes	No		N			
Zinkham[14,15]	No. Europe	(15)	56	Childhood	Yes	Yes						
Zinkham[14,15]	No. Europe	(16)	10	Neonate	Yes	Yes	No		N			
Shahidi[16]	Cen. Europe	(17)	7 B	Neonate	Yes	Yes	Yes		N			
Shahidi[16]	Cen. Europe	(18)	5 B	Neonate	Yes	Yes	Yes		N			
Nordoy[17]	No. Europe	(19)	37	Childhood	Yes		No		N	7 days	Sl↑	Sl↑
Panizon[18]	S. Europe	(20)	1	2/12	Yes	Yes	Yes		Sl↑	5 days	Sl↑	Sl↑
Mohler[19]	No. Europe	(21)	16	2	Yes	Yes	No		N	6½ days	Sl↑	Sl↑
Mohler[19]	No. Europe	(22)	21	6	Yes	Yes	Yes		N	6 days	Sl↑	Sl↑
Mohler[19]	Turkish	(23)	38	16	Yes	No	No			13 days	Sl↑	N
Escobar[20]	?	(24)	59	38	Yes	Yes	No			10 days	N	N
Ben-Ishay[21]	Near East	(25)	38	35	Yes	Yes	Yes		N	10 days		
Ben-Ishay[21]	Near East	(26)	54	52	Yes	Yes			N	6.5-10.5 days		
Ben-Ishay[21]	Near East	(27)	20 F	16	Yes	Yes	Yes		N	7-11 days		
Ben-Ishay[21]	Near East	(28)	34	29	Yes	No	Yes		N	16 days		
Present Case	Cen. Europe	(29)	33	3	Yes	Yes	Yes	Yes (502 g)	N	7.5 days	Sl↑	Sl↑

Key: B = brothers F = female C = cousins N = normal
No., S., Cen. Europe = North, South, Central Europe

and Diamond,[28] however, have reported that one of ten patients studied with proven pyruvate kinase deficiency anemia did not have the markedly increased autohemolysis characteristic of Type II and three of nine who did have the active hemolysis demonstrated substantial improvement after glucose was added.

Primaquine-sensitive Disease

It has been customary to consider the glucose-6-phosphate dehydrogenase deficiency hemolytic disease as distinctly separate from the primaquine-sensitive type.[1-3,20] The justification for this separation, however, is not altogether convincing. Within the drug-induced group, important differences have been established between Negroes and Caucasians. The incidence of primaquine sensitivity is far greater among Negroes[1-3] than Caucasians except for some select groups of Caucasians, e.g., Greeks, Sardinians, Iranians, and non-Ashkenazic Jews.[36] Marks and Gross[37] have shown that the glucose-6-phosphate dehydrogenase activity of the red cells and white cells of affected whites ranged from unmeasurable to markedly low in contrast to affected Negroes whose red cell enzyme is usually about ten per cent of normal and whose white cell enzyme is normal.

Comparing primaquine-sensitive Caucasians with glucose-6-phosphate dehydrogenase deficiency congenital nonspherocytic hemolytic disease patients, all of whom reported thus far having been Caucasians, sharp distinctions are more difficult to define. The congenital group was thought[1-3,15,20] to be unique in that: (1) its members were completely deficient in enzyme, (2) chronic hemolysis was always present and (3) febrile illnesses were more important than drugs in provoking crises. Analysis of these three factors, however, does not strengthen the case for separation of the groups. For example, measurement of enzyme level alone cannot be considered a conclusive distinction, since some Caucasians of the primaquine-sensitive group have also been reported to have no ascertainable level of enzyme, and even one primaquine-sensitive Negro has met this criterion.[26] On the other hand, Kirkman et al.,[9] in describing five cases of the enzyme-deficiency group with clearly measurable, though distinctly low levels of enzyme, suggest that the reason others have been unable to record levels may be simply a question of methodology, dependent on the stabilizing action of the TPN. and mercaptoethanol on glucose-6-phosphate dehydrogenase.

Red Cell Life-Span

Reduction in the red cell life-span of about 25 percent has been well recognized in a substantial proportion of primaquine-sensitive Negroes[1,7,21] but has been studied little in primaquine-sensitive Caucasians. Recently four patients (Cases 25 to 28 in Table 1) have been reported[21] from non-Ashkenazic Jewish groups known to have a high incidence of primaquine-sensitive glucose-6-phosphate dehydrogenase deficiency. All four with proven enzyme deficiency, when studied under relatively normal circumstances, were found to have well-compensated mild hemolytic processes typical of the congenital nonspherocytic hemolytic disease cases. One of these patients developed two bouts of acute hemolytic anemia after febrile illnesses, as have some others[2] in the primaquine-sensitive group, in the characteristic manner of the congenital nonspherocytic hemolytic disease patients. Two of the others developed comparable bouts after treatment with sulfa drugs. As Ben-Ishay and Izak[21] imply, analysis of these four patients, who could readily fit into either the drug-induced or congenital nonspherocytic hemolytic disease category, lends substantive evidence to the concept that enzyme-deficient congenital nonspherocytic hemolytic disease patients and primaquine-sensitive Caucasians manifest variations of a common theme rather than distinct disease entities.

Qualitative Enzyme Distinctions

In challenging the concept of a quantitative difference in the enzyme deficiency between the primaquine-sensitive and the congenital nonspherocytic hemolytic disease groups, Kirkman and co-workers[9] suggest that distinctions may well lie in qualitative differences in the glucose-6-phosphate dehydrogenase involved. Thus far the most striking difference in the enzymes would appear to be the rapidly lost activity of the enzyme on storage in the congenital nonspherocytic hemolytic disease patients compared to the retention of activity by the primaquine-sensitive individuals. Other differences were also noted. It is dubious that the qualitative differences thus far demonstrated warrant a separation between the two groups, but this would appear a most promising area for further investigation. These same investigators[38] have also been able to demonstrate enzyme distinctions between different ethnic groups of glucose-6-phosphate dehydrogenase deficient Caucasians and suggest that a whole spectrum of clinical variants may be the result of such unique enzyme characteristics.

Acid Phosphomonesterase

Recently Oski, Shahidi and Diamond[26] have shown that acid phosphomonesterase is reduced in Caucasians with enzyme deficiency but not in primaquine-sensitive Negroes. The physiologic significance of this finding is open to question. The patient presented in this report had a normal level of acid phosphomonoesterase, refuting the notion that this is an invariable feature of the disease.

Pathogenesis

The mechanism by which the lowered or altered glucose-6-phosphate dehydrogenase predisposes to hemolysis is still speculative, and several carefully derived theories have been proposed.[2,20,39,40] The crux of these arguments is that in a deficiency state of the enzyme there is impairment of the pentose phosphate shunt, which is dependent on this enzyme. Consequently, reduced amounts of TPNH, the end product of the shunt, are formed. Since TPNH is necessary for the production of reduced glutathione, there are decreased amounts of the latter as well. Reduced glutathione has been shown to be necessary for the maintenance of the red cell integrity in several ways, one of which is to protect the cell membrane from oxidative injury as, for example, by drugs. Mohler and Crockett[19] suggest also that with reduced levels of glucose-6-phosphate dehydrogenase in the red cell there is a corresponding diminution in ATP, and that this may play an important causal role in the hemolysis.

Splenectomy

Since his splenectomy nineteen years earlier, our patient has required no further transfusions. He has, however, a chronic, albeit compensated, hemolytic disease. Because he required transfusion only once prior to splenectomy, it is unlikely that he benefited from the operation. Only two of the other 28 cases in the literature had splenectomy, in neither instance with obvious benefit.[8,9]

Thrombocytosis

The thrombocytosis in our patient is believed to be secondary to the splenectomy. Whereas all surgical operations are associated with elevated platelet counts for transient periods,[41] thrombocytosis after splenectomy is more pronounced and more prolonged.[42,43] It would seem reasonable to postulate that the thrombocytosis in this patient predisposed him to thrombotic complications, which in turn produced multiple subclinical pulmonary emboli or pulmonary thrombosis with resultant pulmonary hypertension. This latter would appear well-documented indirectly by radiographic and electrocardiographic studies. A second possibility, either alone or in combination with the thrombocytosis, that could be conducive to thrombosis and consequent pulmonary hypertension is that of thromboangiitis obliterans (Buerger's disease). The markedly reduced peripheral pulsations in all extremities is compatible with this diagnosis. Although neither of the other two cases with glucose-6-phosphate dehydrogenase deficiency congenital nonspherocytic hemolytic disease with splenectomy has had the extensive follow-up that this patient has had, they apparently did not suffer from prolonged post-splenectomy thrombocytosis and thromboembolism.

Treatment

Busulfan was effective in reducing the

platelet level in our patient; but it also inhibited erythropoiesis and leukopoiesis to such an extent as to necessitate the discontinuance of the drug. Instead, the patient has been given prolonged anticoagulant therapy with warfarin sodium. During the two years he has been on this program he has been symptom-free except for one mild episode of traumatic hematuria on cessation of the anticoagulant therapy.

Summary

1. A case of congenital nonspherocytic hemolytic disease with erythrocyte glucose-6-phosphate dehydrogenase deficiency, the twenty-ninth in the world's literature, is reported. The patient, who has the longest post-splenectomy follow-up of the group, has the additional complications of thrombocytosis with multiple bouts of thrombophlebitis and pulmonary hypertension.

2. Most patients are able to compensate for their chronic hemolytic activity, and only at rare times of erythropoietic arrest or hemolytic crisis demonstrate anemia and jaundice. That these episodes are readily managable is attested to by the fact that almost half the cases were diagnosed after the age of thirty.

3. With the exception of certain isolated groups of Caucasians, erythrocyte glucose-6-phosphate dehydrogenase deficiency is far more prevalent among Negroes. In contrast to the Caucasians, Negroes have normal white cell glucose-6-phosphate dehydrogenase. Clinically, the Negro usually presents with self-limited hemolysis after exposure to one of many drugs, but his Caucasian counterpart in either the primaquine-sensitive or congenital nonspherocytic hemolytic disease group can do the same. More characteristically the latter patient manifests his anemia during the course of a febrile illness. All three groups appear to have a chronic hemolytic process of varying severity. Although the Negro usually has a somewhat higher level and the congenital nonspherocytic hemolytic disease patient is usually essentially devoid of erythrocyte glucose-6-phosphate dehydrogenase, the range of deficiency of erythrocyte enzyme has varied considerably in all. Similarities being as apparent as differences between the groups, especially among the Caucasians, it has been suggested that they may be variants of the same disease rather than wholly distinct entities.

4. In the present case, in contrast to previously reported cases of congenital nonspherocytic hemolytic disease with red cell glucose-6-phosphate dehydrogenase deficiency, erythrocyte acid phosphomonoesterase activity was normal.

Acknowledgment

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8-44 May be secured from the author or the reprints.

Some men are not satisfied with the spark of success. They try for an explosion.
— Carey Williams

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For did not the Lord adjure Ezekiel: "And by the river upon the bank thereof, on this side and on that side, shall grow all trees . . . and the fruit thereof shall be for meat, and the leaf thereof for medicine."

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*See Test Your Word Score Page 1411.

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Precautions: Use with caution in patients hypersensitive to sympathomimetic compounds, who have coronary or cardiovascular disease, or are severely hypertensive.

Dextro-amphetamine sulfate: Excessive use by unstable individuals may result in psychological dependence.

Meprobamate: Careful supervision of dose and amounts prescribed is advised, especially for patients with known propensity for taking excessive quantities of drugs. Excessive and prolonged use in susceptible persons, e.g. alcoholics, former addicts, and other severe psychoneurotics, has been reported to result in dependence on the drug. Where excessive dosage has continued for weeks or months, reduce dosage gradually. Sudden withdrawal may precipitate recurrence of preexisting symptoms such as anxiety, anorexia, or insomnia; or withdrawal reactions such as vomiting, ataxia, tremors, muscle twitching and, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, reduce dosage and avoid operation of motor vehicles, machinery or other activity requiring alertness. Effects of excessive alcohol consumption may be increased by meprobamate. Appropriate caution is recommended with patients prone to excessive drinking. In patients prone to both petit and grand mal epilepsy meprobamate may precipitate grand mal attacks. Prescribe cautiously and in small quantities to patients with suicidal tendencies.

Side Effects: Overstimulation of the central nervous system, jitteriness and insomnia or drowsiness.

Dextro-amphetamine sulfate: Insomnia, excitability, and increased motor activity are common and ordinarily mild side effects. Confusion, anxiety, aggressiveness, increased libido, and hallucinations have also been observed, especially in mentally ill patients. Rebound fatigue and depression may follow central stimulation. Other effects may include dry mouth, anorexia, nausea, vomiting, diarrhea, and increased cardiovascular reactivity.

Meprobamate: Drowsiness may occur and can be associated with ataxia; the symptom can usually be controlled by decreasing the dose, or by concomitant administration of central stimulants. Allergic or idiosyncratic reactions: maculopapular rash, acute nonthrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever, transient leukopenia. A case of fatal bullous dermatitis, following administration of meprobamate and prednisolone, has been reported. Hypersensitivity has produced fever, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, stomatitis, proctitis (1 case), anaphylaxis, agranulocytosis and thrombocytopenic purpura, and a fatal instance of aplastic anemia, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity, usually after excessive dosage. Impairment of visual accommodation. Massive overdosage may produce drowsiness lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

Lederle

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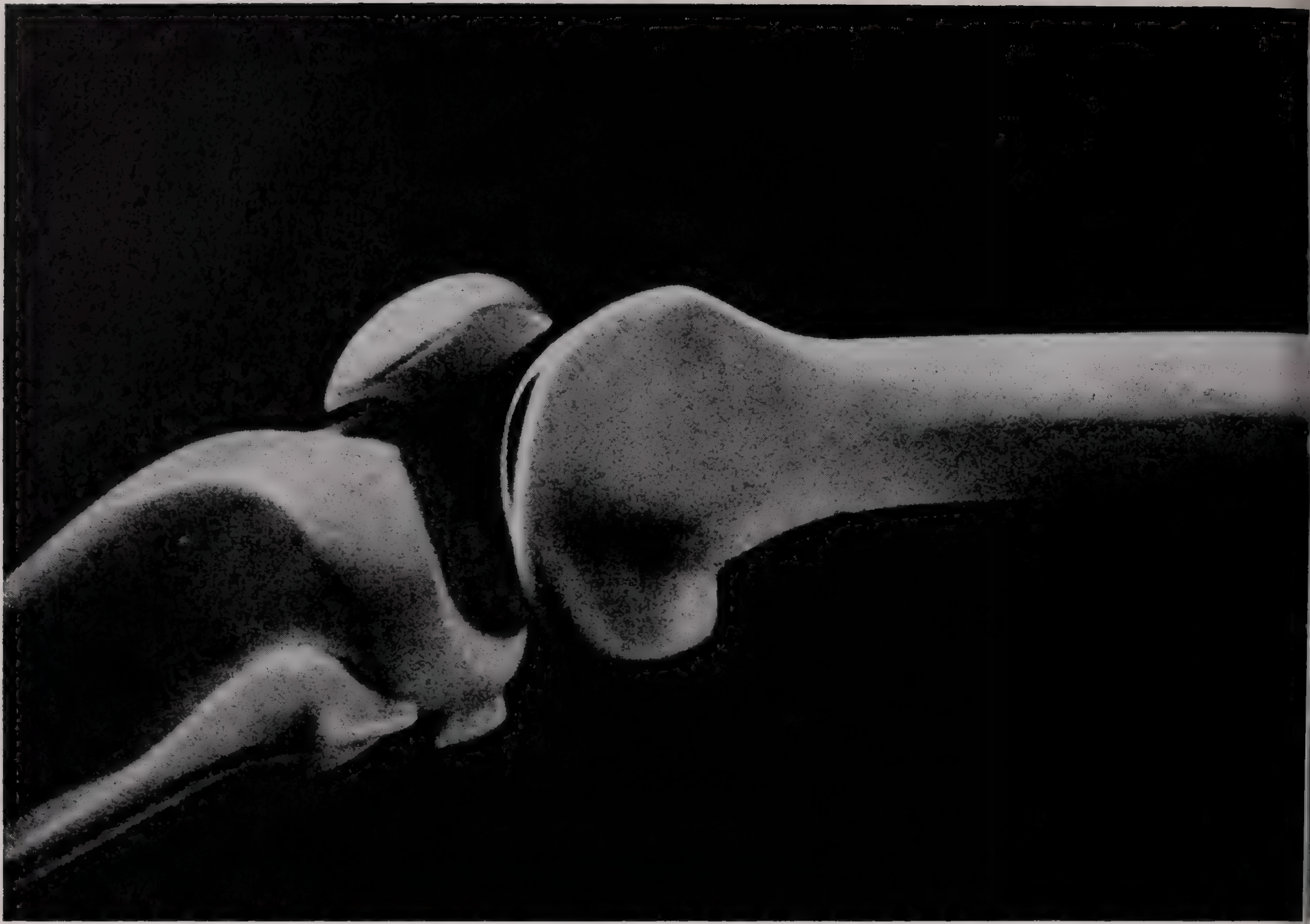

Butazolidin® alka

phenylbutazone, 100 mg.
dried aluminum hydroxide gel, 100 mg.
magnesium trisilicate, 150 mg.
homatropine methylbromide, 1.25 mg.

Usually works within 3 to 4 days in osteoarthritis

The trial period need not exceed 1 week. In contrast, the recommended trial period for indomethacin is *at least 1 month.*

That's why it's logical to start therapy with Butazolidin alka—you'll know quickly whether or not it works. And usually, it will.

A large number of investigators have reported major improvement in about 75% of cases. Some patients have gone into remission. Relief of stiffness and pain may be followed quickly by improved function and resolution of other signs of inflammation. And Butazolidin alka is well tolerated, especially since it contains antacids and an antispasmodic to minimize gastric upset.

Contraindications
Edema; danger of cardiac decompensation; history or symptoms of peptic ulcer; renal, hepatic or cardiac damage; history of drug allergy; history of blood dyscrasia. Because of the increased possibility of toxic reactions, the drug should be used with greater care in the elderly and should not be given when the patient is senile or when other potent chemotherapeutic agents are given concurrently. Large doses of Butazolidin alka are contraindicated in patients with glaucoma.

Warning
If coumarin-type anticoagulants are given simultaneously, the physician should watch for excessive increase in prothrombin time. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Patients receiving such concomitant therapy should be carefully observed for this effect.

Use with caution in the first trimester of pregnancy.

Precautions
Before prescribing, the physician should obtain a detailed history and perform a complete physical and laboratory examination, including a blood count. The patient should be kept under close supervision and should be warned to report immediately fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools. Regular blood counts should be made to guard against blood dyscrasias.

Adverse Reactions
The most common adverse reactions are nausea, edema and drug rash. Moderately lowered red cell count may sometimes occur due to hemodilution. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. Infrequently, agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome or a generalized allergic reaction may occur and require withdrawal of medication. Stomatitis, salivary gland enlargement, vertigo or languor may occur. Leukemia and leukemoid reactions have been reported but cannot definitely be attributed to the drug. Thrombocytopenic purpura and aplastic anemia are also possibl side effects.

Confusional states, hyperglycemia, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, a have hepatitis, jaundice and several cases o anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently.

Dosage
The initial daily dosage in adults is 300-600 mg. daily in divided doses. In most instances 400 mg. daily is sufficient. When improvemen occurs, dosage should be decreased to the minimum effective level: this should not exceed 400 mg. daily, and is often achieved with only 100-200 mg. daily.

For complete details, please refer to full prescribing information.
6509-V(B)

Also available: Butazolidin®, phenylbutazone Tablets of 100 mg.

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Editorials

Treatment of the Anovulatory Syndrome

ONE OF THE major problems confronting a physician who is interested in reproductive disorders relates to the failure of ovulation. Anovulation is a basic defect in the Stein-Leventhal syndrome,* various disorders of the adrenal gland, pituitary and hypothalamic disorders, nutritional abnormalities including liver disease, hypothyroidism, various psychologic disturbances and dysfunctional bleeding. Therefore the first step towards effective therapy is arriving at an accurate diagnosis, and each patient must be treated according to the etiological factors involved.

Elsewhere in this journal** the "stages of development" of the treatment of the anovulatory syndrome are discussed and the impression is conveyed that all methods tried previous to clomiphene were either unsuccessful or dangerous and should be discarded. Clomiphene may represent the long-sought-for substance capable of inducing ovulation in the human, but at the moment this awaits confirmation. Clomiphene citrate is an experimental drug and available only at certain research centers. Until this medication is released for general use, the practicing physician must continue to rely on less specific methods for induction of ovulation.

There are several general methods that may still be advocated for the production of ovulation. Steroids may trigger pituitary function, or cyclic estrogen and progesterone therapy may completely suppress the pituitary and produce a rebound phenomenon with ovulation when stopped. Intravenous administration of conjugated estrogen has been shown to effectively induce ovulation in nearly half of the patients who fulfill the criteria of adequate proliferative phase activity. The academician points out that there is no justification for administration of thyroid hormone to the euthyroid individual. Yet the clinician has frequently seen cases of irregular, anovulatory bleeding converted to a regular, ovulatory pattern by raising the thyroid function, as measured by the PBI., from the low normal to the high normal range. The close relationship of ovarian function and even low normal thyroid function should not be minimized. Low-dosage irradiation of the ovaries has been proved to be extremely effective in inducing ovulation. Although third and fourth generation follow-up studies have failed to detect genetic abnormalities, this method has been nearly abandoned, because of this potential hazard.

Since all of these methods are readily available, little would be lost by attempting to induce ovulation before referring a patient to a research center.

The ideal patient for clomiphene therapy is one who is anovulatory with adequate

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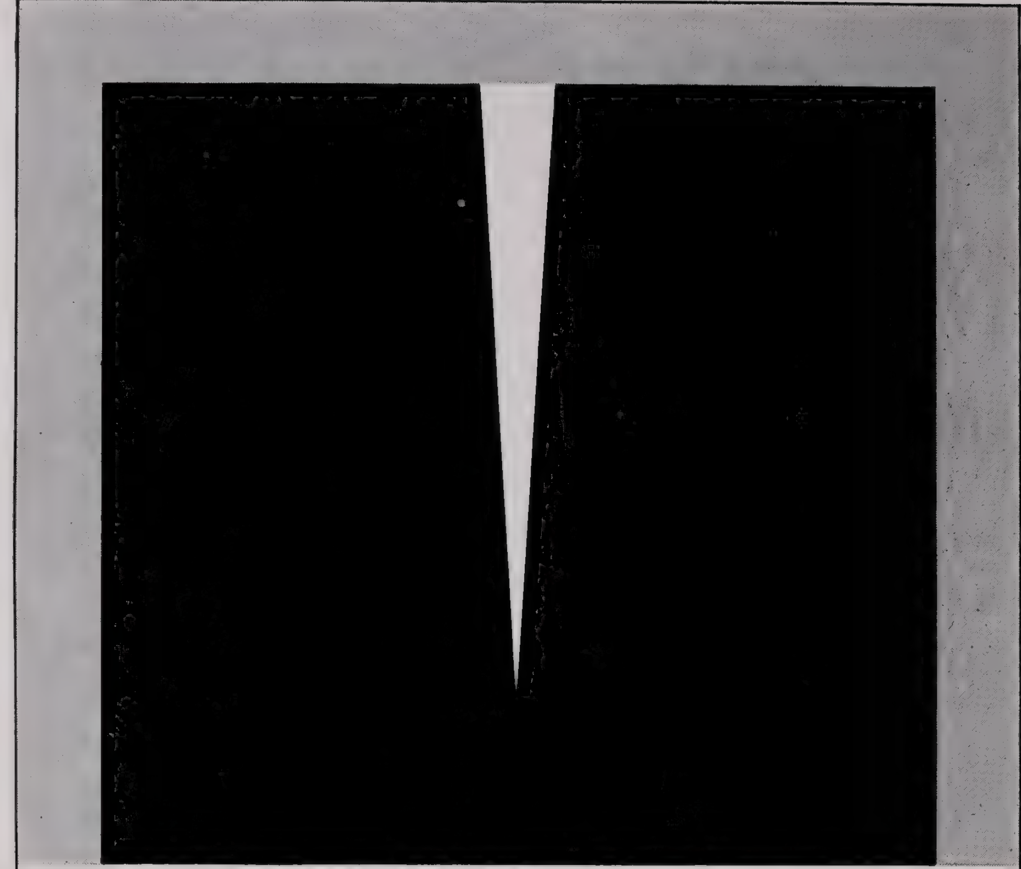
*See Minnesota Med 46:1215, 1963.

**See Page 1357.



incisive

A good way to describe 'Stelazine'. It's different from the tranquilizers that sedate and dull your anxious patients. Its antianxiety effect is direct. On 'Stelazine', your patients can be calmed yet remain alert.

And 'Stelazine' offers additional benefits. Dependence has not been reported. At low doses, side effects are minimal. Its b.i.d. dosage is convenient and economical.

Stelazine®
brand of **trifluoperazine**

The following is a brief precautionary statement. Before prescribing, the physician should be familiar with the complete prescribing information in SK&F literature or *PDR*. *Contraindications:* Comatose or greatly depressed states due to C.N.S. depressants and in cases of existing blood dyscrasias, bone marrow depression and liver damage. *Precautions:* Use with caution in angina patients and in patients with impaired cardiovascular systems. Antiemetic effect may mask symptoms of other disorders. An additive depressant effect is possible when used with other C.N.S. depressants. Prolonged administration of high doses may result in accumulative effects with severe C.N.S. or vasomotor symptoms. Use in pregnant patients only when necessary for the patient's welfare. *Side Effects:* Occasional cases of mild drowsiness, dizziness, mild skin reactions, dry mouth, insomnia and amenorrhea. Neuromuscular (extrapyramidal) reactions (motor restlessness, dystonias, pseudo-parkinsonism) may occur and, in rare instances, may persist. In addition, muscular weakness, anorexia, rash, lactation, hypotension, and blurred vision have been observed. Blood dyscrasias and cholestatic jaundice have been extremely rare.

For a comprehensive presentation of 'Stelazine' prescribing information and side effects reported with phenothiazine derivatives, please refer to SK&F literature or *PDR*.

Smith Kline & French Laboratories, Philadelphia SK&F

endogenous estrogen but in whom sufficient and cyclic stimulation of pituitary gonadotrophic function is lacking. Best results will be obtained in treating patients with the Stein-Leventhal syndrome, and success can be expected in a high percentage of patients with secondary or hypothalamic amenorrhea. A patient with a reduced estrogen level, such as the one presented by Spellacy and Cohen, will have a less favorable prognosis for subsequent ovulation.

Paul N. Larson, M.D.
Minneapolis, Minnesota

Manifestations of Cancer

THE COMMONEST manifestations of cancer are related to local growth of the tumor which leads to pain, bleeding, or interference with the normal function of organs involved by the primary neoplasm or its metastases.

In its advanced stages cancer becomes a systemic disease as metastases involve diverse systems and as the growth of the tumor interferes with the nutrition of the patient. Apart from these common systemic effects, however, cancer may at times produce symptoms remote from the site of primary or metastatic tumor and not explicable on a simple mechanical basis.

The article of Nuessle in the April* issue of MINNESOTA MEDICINE catalogues these effects. Some, for example, certain of the endocrine disturbances, are clearly related to the synthesis of hormonal substances by the tumor itself. On the other hand, the mechanism responsible for such manifestations as the remote neurological syndromes of cerebellar dysfunction or peripheral neuropathy remains speculative.

Its systemic manifestations may provide an opportunity for early diagnosis of cancer and thus lead to more fruitful therapy. Thus recognition of the significance of hypertrophic osteoarthropaty, acanthosis nigricans, or migratory thrombophlebitis is far from academic. In other instances correct recognition is important as the manifestations themselves may be susceptible to rational symptomatic therapy even if the tumor itself cannot be effectively controlled.

Paul D. Redleaf, M.D.
St. Paul, Minnesota

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*See Minnesota Med 49:659, 1966.

Use of Phenothiazine Compounds During Labor

THE INCESSANT search for medications to induce calmness and cooperativeness during labor as well as to potentiate the pain-relieving actions of narcotics has lead to the widespread use of the phenothiazine compounds.

These compounds have been studied extensively in relationship to their known ability to produce circulatory and respiratory depression, confusion, prolongation of anesthesia, and, under some circumstances, extrapyramidal motor symptoms. From these studies the drugs have been determined to be safe for both the mother and the infant. Drs. Diamond, Tietz, and Spellacy* have contributed further to our knowledge of the safety of one of the phenothiazines, promethazine, by evaluating its potential ability to produce increased levels of serum bilirubin in the infant by its cholestatic mechanism. Their study indicates that promethazine given during labor does not raise the incidence of bilirubinemia in the newborn infant.

In a double-blind study my colleagues and I have evaluated promethazine and hydroxyzine for meperidine potentiation and anxiety relief during labor in approximately 300 patients with term infants. In evaluating the infants three and four days after birth, we found that the incidence of neonatal jaundice was identical in infants of mothers who had received either compound. This study will be reported in detail at a later date. Data from our study, however, indicate that promethazine causes no increase in serum bilirubin levels of infants when given to their mothers during labor.

George D. Malkasian, Jr., M.D.
Rochester, Minnesota

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*See Minnesota Med 49:1213, 1966.

when agitation

accompanies

spasm of the

'G. I.' tract.

Butadonna(TM)

BUTABARBITAL SODIUM 15 MG (BARBITURIC ACID DERIVATIVE)
WARNING: MAY BE HABIT FORMING
BELLADONNA EXTRACT (TOTAL ALKALOIDS 0.188 MG.) 15 MG

provides gentle,

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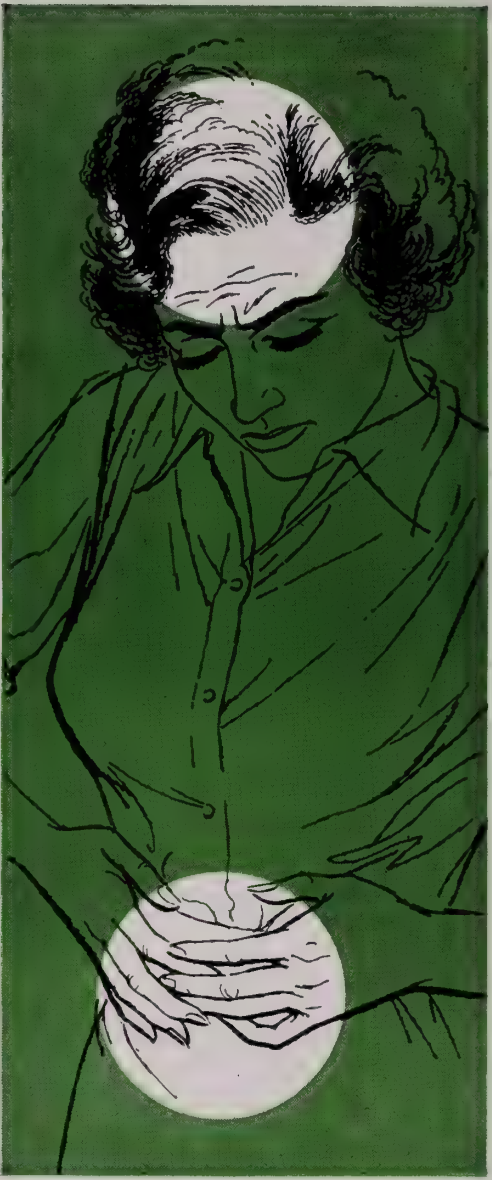
relaxes 'G. I.' spasm.



Butadonna quiets the "brain-on-gut" influences by providing the smooth, intermediate sedative, butabarbital sodium, desirable in combination with the proven antispasmodic, belladonna extract. Butabarbital sodium is more rapidly eliminated than phenobarbital, and avoids the latter's cumulative effect.

Indications: Antispasmodic-sedative. Useful in the treatment of peptic ulcer, gastritis, duodenitis, irritable colon syndrome, ulcerative colitis, regional enteritis, and other conditions associated with gastrointestinal spasm. Also may be useful in functional dysmenorrhea.

Usual adult dosage is one tablet 3 or 4 times daily as needed.

Caution: Contraindicated in glaucoma and urinary retention. Reduce dosage or discontinue use in event of blurring of vision, dryness of mouth, tachycardia, or excessive drowsiness. Continued use of butabarbital sodium may be habit forming.

Cole

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The Parathyroid Saga

A THIRTY-EIGHT-YEAR-OLD streetcar conductor started having leg pain in 1921. For five years a host of treatments were attempted, including mercurials for syphilis. Finally, x-rays revealed Von Recklinghausen's disease (osteitis fibrosa cystica generalasata).

In December of 1924 the inevitable happened; the patient broke his leg. Until that time a dialogue had been going on in the endocrinologic world concerning the parathyroid adenomas seen in von Recklinghausen's disease. The generally held view was that these tumors were secondary, a response to demineralization of the skeleton. Further, they were considered a salutary effort on the body's part to compensate for the loss of calcium from the bones. Patients with the disease were treated with quantities of crude animal parathyroid extract. On the basis of the then current theory, Felix Mandl tried an experiment; he transplanted human parathyroid tissue into the patient's neck. There was no improvement. He kept on breaking bones and by July of 1925 had very little skeleton left. Then Mandl reversed his field 180 degrees. He reoperated on his patient's neck and removed a large parathyroid adenoma. The patient got better.

The following is a brief resume of the anatomic, pathologic, and physiologic data that provided Mandl with the impetus to explore the patient's neck. Ivar Sandstrom discovered the parathyroids in 1880. In 1891 von Recklinghausen described his bone disease. In 1896 Vassale and Generali showed that removal of the parathyroids caused tetany. At autopsy in 1903 Askanazy demonstrated a parathyroid tumor in a patient with von Recklinghausen's disease. Next, Jacob Erdheim performed an elegant series of investigations, concluding that calcium is not deposited in the teeth of rats in the absence of parathyroid hormone. From 1907 through 1914 other critical experiments showed that there was parathyroid hypertrophy in rickets as well as in osteomalacia (adult rickets). It had been repeatedly demonstrated that parathyroid adenomas were present in von Recklinghausen's disease, presumably compensatory, like the enlargement of the gland in rickets. The problem turned on the issue of distinguishing osteomalacia from osteitis fibrosa cystica.

All of the above took place in Europe. Meanwhile in America in 1900 Jacques Loeb discovered the role calcium plays in muscle contraction. Hanson and Collip extracted parathyroid principle in 1924. Isadore Greenwald discovered that the Hanson and Collip material puts animals into negative calcium balance. In 1926 Eugene DuBois, studying a certain Captain Martel who kept on breaking bones and passing renal stones, found entirely too much calcium in his blood. The patient was eventually seen by Doctors Albright, Aub and Bauer of The Massachusetts General Hospital. After six operations on the patient's neck, the mediastinum was explored and a tumor removed. Unfortunately the patient never recovered, succumbing to complications of that rather daring procedure for the times.

In the July issue of MINNESOTA MEDICINE Doctors Winter and McQuarrie's report* serves to remind us of the variability in the clinical manifestations of this disease. We are now asked to consider the diagnosis in patients with a variety of gastrointestinal complaints ranging from intractable ulcer disease to chronic relapsing pancreatitis. Thus the story which began in 1880 with the discovery of parathyroids is far from over.

Robert Maslansky, M.D.
Minneapolis, Minnesota

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*See Minnesota Med 49:1061, 1966.

Forgiveness is the fragrance the violet sheds on the heel that has crushed it.
— Mark Twain

SQUIBB NOTES ON THERAPY

Breast-feeding and the "modern mother"

Despite a mild resurgence of interest in the importance of breast-feeding a few years ago, many women today do not choose to nurse their young. This is for a variety of reasons—social, economic, cultural and sometimes medical. In such cases the physician's task is to find the most suitable means of preventing lactation and easing the pain of breast engorgement.

The means of therapy

The value of hormone therapy for this indication is of course well established. Both androgen and estrogen are known to inhibit the production and secretion of the lactogenic hormone by the anterior pituitary. As estrogen levels decline sharply at parturition, lactogenesis is established. When androgen and estrogen are administered to the patient before the release of the lactogenic hormone lactation and breast engorgement are usually prevented.

The time of therapy

The time of administration of this combined medication is crucial; it must be given early enough to suppress the pituitary prolactin and last long enough to permit physiologic readjustment during the puerperium. Excellent results are most often seen when therapy is administered before the onset of the second stage of labor.

However, factors other than effectiveness must also be considered. The agent selected should not interfere in any way with parturition, subsequent uterine involution and the restoration of normal ovarian cyclic function. Furthermore, it should not cause rebound breast engorgement or other manifestations of hormonal imbalance.

A balanced formulation

Providing single-dose therapy for the prevention of lactation and breast engorgement, Deladumone OB is a potent androgen-estrogen combination with a prolonged action. The optimal balance of androgenic and estrogenic hormones achieved in this preparation minimizes the disadvantages inherent in single hormone therapy, such as rebound breast engorgement. Involution of the uterus and resumption of menstrual cycles are not affected.

As reported in a recent published study (Roser, D. M.: Obstet. & Gynec. *27*:73, 1966), Deladumone OB provided good suppression of breast engorgement in 95.3% and suppression of lactation in 81.1% of 86 obstetrical patients. These results are in general agreement with those of many earlier investigations; in several studies this injectable androgen-estrogen combination proved to be superior to oral medication.

Dosage:

As a single injection of 2 cc. before the onset of the second stage of labor.

Contraindications:

Established or suspected mammary cancer or genital malignancy.

Precautions and Side Effects:

Certain patients may be unusually responsive to either estrogenic or androgenic therapy. In such individuals virilization, uterine bleeding or mastodynia may occur.

Supply:

Deladumone OB, providing 180 mg. testosterone enanthate and 8 mg. estradiol valerate per cc., is available in 2 cc. Unimatic® disposable syringes and in 2 cc. vials. Both preparations are dissolved in sesame oil, with 2% benzyl alcohol as a preservative. *Before use, consult product literature for full prescribing information.*

Deladumone® OB

Squibb Testosterone Enanthate (180 mg./cc.) and Estradiol Valerate (8 mg./cc.)

Single-dose injection for lactation inhibition

SQUIBB *'The Priceless Ingredient' of every product is the honor and integrity of its maker.*

Intraspinal Arteriovenous Anomalies

In the February issue* of Minnesota Medicine a preliminary report appears on the surgical treatment of intraspinal arteriovenous anomalies.

Although arteriovenous malformations of the spinal cord are rare when contrasted with their occurrence in the brain, the condition can be diagnostically perplexing. The sites in the spinal cord that are most often affected are found to be the lower thoracic to the upper lumbar segments and the cervical enlargement.

These malformations may bleed spontaneously or rupture with trauma, resulting in bleeding into the subarachnoid space or into the substance of the cord. They may be confused with subarachnoid bleeding from an intracranial source, but can usually be differentiated by evidence of spinal cord involvement. When bleeding takes place within the cord, there is an abrupt onset of symptoms with intense pain in the back followed shortly by a flaccid paralysis and loss of sensation below the level of the lesion.

Other symptoms may arise from compression of cord structures or by thrombosis leading to ischemia or infarction of the adjacent cord parenchyma. This latter event may, of course, occur episodically, leading the diagnostician to consider a demyelinating disease such as multiple sclerosis because of the relapsing nature of the symptoms.

Too often this condition cannot be differentiated from other processes leading to progressive spinal cord symptomatology until myelography is carried out revealing a pulsatile, tortuous mass extending over many cord segments. Aortography can better delineate the malformation, provided that the feeding blood vessels are of a size sufficient to be visualized radiographically.

Earlier reports about the benefits of the surgical treatment of such lesions have been pessimistic. This pessimism arose from the knowledge that these vascular malformations usually lie within the cord as well as upon its surface and that the blood supply to the spinal cord is a tenuous one.

The anterior spinal artery is throughout much of the length of the spinal cord a slender longitudinal chain of anastomosing vessels formed by ascending and descending radicular arteries. At the thoracic segments Tl-4 and the first lumbar cord segment the anastomoses are meager, leaving these areas especially vulnerable to any interference with their vascular supply. Arteriovenous malformations are capable of altering the normal hemodynamics of an area by their shunting of arterial blood directly into the venous system, thereby depriving the tissue of its normal blood supply. Under these circumstances one wonders if further damage to the cord parenchyma may not occur following the ligation of the arterial feeders to the malformation.

Paul Silverstein, M.D.
Minneapolis, Minnesota

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*Love, J. Grafton, Svien, Hendrik J., Baker, Hillier L., Jr., and Layton, Donald D.: Intraspinal Arteriovenous Anomalies. Minnesota Med 49:255, 1966.

Hepatolobectomy for Metastatic Malignancy

Hepatolobectomy for metastatic malignancy is a controversial subject, to say the least. The opportunity to make such an operative decision is not likely to present itself even once a year to most surgeons.

In the case of the four-year-old boy with metastatic neuroblastoma, Drs. Brown and Hart* have given a clear and concise, yet detailed account of a complicated problem and also an excellent description of the operational procedure. While the outcome was disappointing, many lessons can be learned from a study of the report.

Neuroblastoma is one of the most unpre-

Continued

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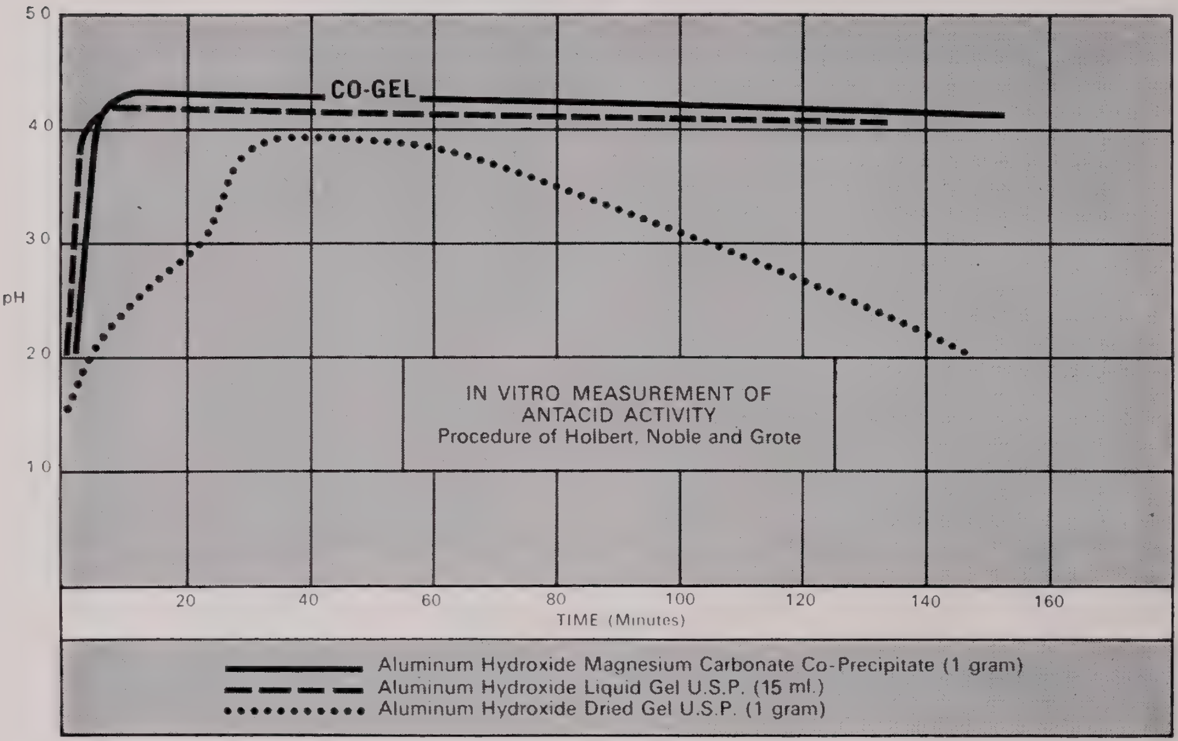
*Brown, Paul M., and Hart, Joseph T.: Total Right Hepatolobectomy for a Metastatic Neuroblastoma. Minnesota Med 49:591, 1966.

CO-GEL

THE NEW ANTACID



Holbert, J. M., Noble, N., and Grote, I. W.—Jnl. Amer. Pharm. Assoc. (Sci. Ed.) 37,292 (1948).

Now, an antacid tablet with the effectiveness of a liquid!

CO-GEL is not just another antacid, but rather it's an entirely *new antacid compound* for gastritis, hyperacidity and peptic ulcers. It is an Aluminum Hydroxide formulation with Magnesium Carbonate Co-Precipitate. The Co-Precipitate, a new chemical, gives CO-GEL Tablets the speed of action and the duration of a liquid antacid.

The above chart compares the antacid action of the COGEL Tablet formula with both liquid and dry $Al(OH)_3$. Notice that CO-GEL neutralizes acid faster than $Al(OH)_3$ dried gel tablets and has a prolonged buffering action. The CO-GEL curve parallels that of liquid $Al(OH)_3$.

Liquid CO-GEL, containing the Co-Precipitate, is also available. CO-GEL is reasonably priced to the patient. Availability: CO-GEL Tablets (bottles of 100 and 1,000) CO-GEL Liquid (pints and gallons).

For complete information and samples, write to Dept. MM-105.

FORMULA

Each CO-GEL Tablet, and teaspoonful of CO-GEL Liquid, contains 330 mg. of Aluminum Hydroxide Magnesium Carbonate Co-Precipitate. Tablets have a chewable base. Both forms are mint flavored.

CONTRAINDICATIONS

None.

DOSAGE

For relief of hyperacidity, peptic ulcers or gastritis, chew one tablet (or take one teaspoonful). Repeat in 1 hr. if necessary.

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dictable of malignant lesions. Many instances of cure have been reported after only limited operative manipulations ranging from simple biopsy to an unsuccessful attempt at total removal. In other cases the apparent cure has been attributed to x-ray therapy, to chemotherapy with agents as innocuous as vitamin B_{12}, or to both methods.

Metastasis to the liver and other viscera has been known to disappear completely under various forms of therapy or, surprisingly, even in the absence of therapy. Skeletal metastatic lesions, however, have been much less accommodating.

It is this unpredictability of neuroblastoma which gives hope to both patients and physicians and encourages such a strenuous undertaking as hepatolobectomy.

Much has been written about the beneficial effects of preoperative irradiation. Temporary reduction in size is an obvious and measurable result in most cases. The implication usually has been that such irradiation makes the surgeon's task much easier. In my own experience with preoperative irradiation, the difficulties often seem greater than usual, due to bleeding, adhesions, and a tumor which is partially necrotic and friable, and often disintegrates on manipulation. Thus, preoperative irradiation invariably leads to speculation as to what effect delay, therapy, and extra manipulations and examinations may have on the spread of the first malignant cells.

For me, one unmentioned value of preoperative irradiation has been a sense of aggressive confidence, knowing the family is emotionally prepared for a strenuous attack on an often hopeless problem. Only rarely does a patient receive irradiation without conclusive and confirmed diagnosis. Consequently, the family is emotionally prepared much the same as they are prepared for a "second look" or "redo" operation. This emotional adjustment is rarely present with the exploration for "suspected" malignancy; consequently the operative measures are possibly less heroic than in the other situations mentioned.

The transplantation of hepatic tissue is now mechanically feasible, and only the mysteries of host rejection still seem to hinder successful substitution. Since the liver functions so well even when massively replaced with malignant tumor, successful transplantation will more likely be considered in cases in which the liver has been destroyed by infection or benign tumor processes. Reports are now appearing of attempts to remove a portion of a widely disseminated malignant tumor and reimplant it in the host after various treatments outside the body. Although it is too early to be optimistic, there is hope.

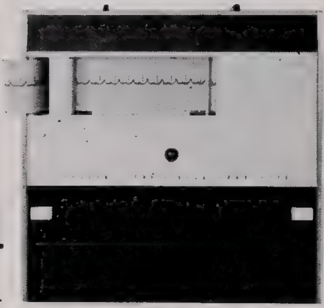
The whole philosophy of the management of malignant lesions in children is changing. Certainly palliation must be viewed differently in a four-year-old child than in a 64-year-old adult. In a four-year-old patient the primary objective is obviously complete cure; failing this, palliation is directed only toward relieving pain and comforting the parents. Once it becomes obvious to all concerned that cure is no longer possible, any treatment which merely prolongs life or elevates the level of consciousness seems unjustified. Fortunately, each day brings some new glimmer of hope for the otherwise hopeless problems. Malignant lesions of many types are showing sufficient response to chemical agents to be encouraging. The plight of a four-year-old suffering from uncontrollable diabetes mellitus probably appeared just as hopeless in 1920 as does that of the four-year-old with a metastatic malignancy today.

Since hope springs eternal in the hearts of parents, it is our obligation to do everything humanly possible to restore health. Once the case is terminal, we are equally obliged to see that death is not robbed of its dignity.

Hugh B. Lynn, M.D.
Rochester, Minnesota

Enjoy when you can, and endure when you must. — Goethe

if you've ever had to hunt for
your ECG cables, straps, electrodes
...pull out the wall plug
and reverse it...struggle with
paper that wouldn't thread
...or needed a faster chart
speed or different sensitivity...



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Reverse power line polarity on 500 by pushbutton.

Reload Permapaper chart rolls with no threading, in seconds (one roll makes 25 12-lead tests).

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All 500 Viso's have 25 and 50 mm/sec. chart speeds . . . ½, 1 or 2X sensitivity settings for optimum trace amplitude.

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Amputation of Lower Extremity

THE DECISIONS when and at what level to amputate the lower extremity are of equal importance. It is desirable to save all viable tissue; however, the best level for efficiency of a prosthesis demands consideration. The degree of trauma frequently determines the level. When to operate may be an even more serious immediate problem.

(A) I recall a news report in a San Antonio paper that an airplane had crashed and that the pilot was so badly injured that a bilateral thigh amputation was performed. I made the statement at the time that the next day's paper would state that the pilot did not survive his surgery—and it did.

(B) A patient's family demanded that I see an elderly gentleman on the way to the operating room for amputation of a traumatically injured leg. The patient was in shock with a blood pressure of 50. A tourniquet was applied immediately above the injury, and the distal extremity encased in dressings saturated with 10 per cent formaldehyde solution. He received urgent immediate shock treatment and blood replacement. Several days later when he was in good condition the leg was amputated uneventfully at the level of the upper border of the tourniquet.

The temporary tourniquet procedure is reported to have been employed by the Chinese many years ago where soldiers could not receive surgical attention for days and required many miles of transportation.

My first experience with the temporary tourniquet amputation was when I was assistant to Dr. R. E. Farr. A young man was in a very critical condition due to gas gangrene infection superimposed on an extensive arm injury. The same procedure was employed. Gangrene did not advance above the tourniquet. An amputation was performed uneventfully a week later.

The level of amputation in patients with endarteritis obliterans may present a problem. We have seen patients who first had a toe removed, later a calf amputation, and finally an amputation at a viable level.

If an occluding embolus is present and is not removed, pulseless vessels and discoloration soon reveal the level of viability.

The aged patient with obstructing arteriosclerosis, with diabetes, or coronary disease presents a challenge. Amputation and reamputation are not uncommon. Failure of an operation below the knee leads to additional hazard if a thigh amputation becomes necessary.

During more than 50 years in the training for surgery and its practice I have had an unusual experience with amputation, based on my use of the temporary tourniquet procedure together with my use of local anesthesia in very hazardous cases.

The methods which Dr. Henry Wessman* described to determine the adequacy of the circulation of a lower extremity with regard for the vascular efficiency can be of great value in pathological arterial obstruction.

When to operate and at what level to amputate demand necessary consultation, experience, and above all good surgical judgement.

Stanley R. Maxeiner, Sr., M.D.
Minneapolis, Minnesota

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*Wessman, Henry C.: Selecting the Amputation Site in the Lower Extremity with Regard for the Vascular Efficiency. Minnesota Med 49:587, 1966.

Importance of Prompt Correction of Anemia in Infants*

THE IMPORTANCE OF prompt correction of anemia as severe as noted in this case is emphasized by the fact that true heart failure developed. The cautious administration of packed erythrocytes might have averted the failure, because this would have given effective cells to carry much-needed oxygen. The increasing size of the liver is the most striking evidence for cardiac failure, as it

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*Searl, Richard H., and Speckhals, Robert C.: Severe Anemia as a Cause of Heart Failure in Infancy. Minnesota Med 49:911, 1966.

what time is it?

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of active tuberculosis
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four thousand
of U.S. population.

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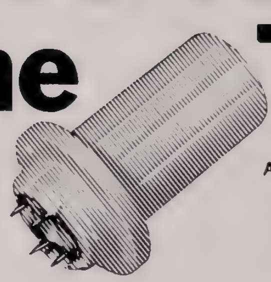

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appeared in this case or might appear during the administration of packed erythrocytes. Although it is generally believed that digitalis is of little benefit in congestive heart failure accompanied by severe anemia, Fowler et al.[1] showed that it is effective.

The one striking factor in the causation of anemia in this child was an inadequate dietary intake of protein and iron. The weight gain was not excessive, the mother was not anemic, and there was no apparent blood loss in the stools. Ferrous sulfate is indeed the most effective form of treatment; although other ferrous preparations may be more palatable, they are not so effective. One can consider intramuscular injection of iron in cases of severe anemia, a type of treatment that gives a more prompt increase in the hemoglobin concentration and, if the anemia is not so severe that cardiac failure is a threat, might eliminate the need for transfusions.

Anemia of this degree can be avoided if one is especially alert for it in premature infants or in children from mothers who are anemic or who have had multiple pregnancies; particularly, the problem of excessive milk intake should be kept in mind. As the infant approaches five to six months of age, iron-containing foods should be included in the diet (cereal, egg yolk, and meat). Then as the child approaches eight to 10 months of age, weaning it from the bottle to the cup will promote a greater intake of meat, vegetables, and other foods which contain a higher percentage of iron.

E. Omer Burgert, Jr., M.D.
Rochester, Minnesota

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1. Fowler, N. O., and Holmes, J. C.: Dextran-Exchange Anemia and Reduction in Blood Viscosity in the Heart-Lung Preparation: With an Observation Upon the Action of Ouabain in Anemic Heart Failure. Amer Heart J 68:204, 1964.

Test Your Word Score

Anima mundi — *the soul of the universe* (page 1363).

Redoubt — *retreat* (page 1373).

Skeletonized — *dissected from surrounding tissue* (page 1377).

Loins — *biblical: that part of the body to be girded* (page 1386).

Primaquine — *an antimalarial agent* (page 1387).

Vulneraries — *agents that promote wound healing* (page 1395).

Thrombocytopenia — *abnormally small number of platelets* (page 1458).

Cryptogenic — *of obscure, indeterminate origin* (page 1464).

Atopic — *possessing a form of allergy or hypersensitiveness* (page 1483).

Antinomian — *against morality — the moral law is useless; faith alone is necessary for salvation* (page 1491).

Paradoxical — *seemingly contradictory* (page 1510).

A Great Platitude

Rare is the meat that is uncooked.

BE A MYTH-MONGER #3

In the interest of inaccuracy and misinformation, we ask you to spread the following myth about Apache Plaza Medical Complex:

APACHE PLAZA MEDICAL COMPLEX IS ON THE NORTHEAST EDGE OF MINNEAPOLIS. EVERYBODY KNOWS THAT PEOPLE IN THAT AREA ARE POOR CREDIT RISKS.

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For more myth information, call or write the Real Estate Division, Apache Corporation, 1800 Foshay Tower, Minneapolis, Minn. 55402. Telephone: (612) 339-7781.

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BE A MYTH-MONGER #4

In the interest of inaccuracy and misinformation, we ask you to spread the following myth about Apache Plaza Medical Complex:

DOCTORS!! APACHE PLAZA'S MEDICAL COMPLEX DOES NOT HAVE A HOSPITAL NEXT TO IT.

True enough, it doesn't. The closest hospitals to Apache Plaza Medical Complex are from 9 to 15 minutes away. But then again, we must remember . . . over 95 per cent of a doctor's patients do not require hospitalization. By relocating adjacent to a hospital, you might put a geographic imposition on your patients, as well as your previous hospital commitments.
Doctor . . . as a matter of fact, Apache Plaza is the center of the community for all of northwest St. Paul, northeast Minneapolis, and suburbs.

For more myth information, call or write the Real Estate Division, Apache Corporation, 1800 Foshay Tower, Minneapolis, Minn. 55402. Telephone: (612) 339-7781.

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The Editor's Soliloquy

The Human Paradox

We love the individual but we hate the group. We trust our friend but we are skeptical of his. We can always find an isolated exception to disprove the rule while we often question the validity of overwhelming evidence.

En masse, the plumber, the carpenter, the mechanic et al. are bunglers and charlatans, whose charges are exorbitant for a twist of a mere screw and who 'discover' things to repair that we never even knew existed; whereas the architect who designed our particular house or the engineer who devised our favorite car must have been a paragon of ingenuity; else how could the house have stood up so sturdily or the car have functioned so smoothly for so long!

In the opinion of the layman even doctors fall collectively into the category of a suspect group. Each physician of us singly is a dedicated humanitarian; in the aggregate we constitute a coldly calculating and venal fraternity.

No one who knows me, the individual doctor, hates me; but many hate the medical profession in general. They resent our steady nerve but endorse our courage in a crisis; they laud our integrity but deprecate our refusal to compromise by so much as an iota.

They praise our meticulous office and the bevy of nurses who keep it spotless; but they criticise the fees required for the purpose. They are humbly flattered to be attended to without a nickel in their pockets; but they airily ignore the month-after-month statement that arrives and too often remains in the windowed envelope to augment their pile of unpaid bills.

They return to the doctor who prescribes a self-perpetuating list of ineffectual remedies but go elsewhere if he points out that a physiologic process must run its inexorable course. They beam on the doctor who agrees that their massive overweight is 'just right' but accuse him of having no understanding of their energy requirements if he suggests that they would feel better trimmed down.

They are 'forever grateful' to the doctor who 'pulled them through' a complicated postoperative convalescence; but they are nettled for having been dismissed from the hospital on the third postoperative day. They appreciate his generosity if he keeps them on compensation for a few weeks beyond the recovery period but consider him heartless if he recommends work as the best physiotherapy.

All in all, as hostages to fortune from birth to death, they find us doctors indispensable and irreplaceable; but they wish they didn't.

So it goes with the human species vis-a-vis its doctors and other professional, political, economic, and social brotherhoods. The so-called lower animals are distinguished for their simplicity, consistency, and directness. Why must mankind alone be devious, oblique, and perverse? Why must paradox be the hallmark of Homo sapiens?

If you can figure it out let me hear from you. I'll be waiting!

Carl O. Rice, M.D.

Mom says: A "blueblood" is nothing more than a man with a lot of "greenback."
— C. O. R.

The population explosion

Chomp. Chomp. Chomp. He's off again on another spree of second helpings.

Tomorrow, crash! He'll be on a newfangled diet. Starving himself.

He's just one of the many who bounce between starvation and overeating, and with every rebound make losing weight more difficult.

As a professional, you can help. First by pointing out that skipping meals is no solution, and second by recommending long-range weight control through sensible eating habits and nourishing foods. Every day. Day after day.

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Project Weight Watch has been initiated to assist you. Its scope is nationwide, its purpose is to focus professional attention on the problem.

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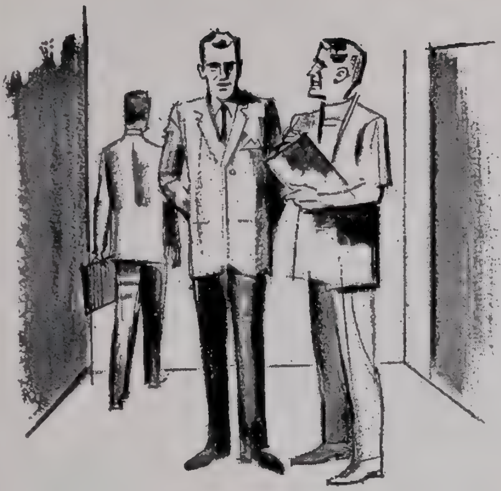

Curbstone Consultation

QUESTION: What triad of laboratory tests can be ordered to assist in diagnosing pulmonary embolism and infarction, and differentiating them from pneumonia and acute myocardial infarction?

ANSWER: Patients with pulmonary embolism or infarction usually have an elevated serum lactic dehydrogenase (LDH) and serum bilirubin, but their serum glutamic oxaloacetic transaminase (SGOT) remains normal. This combination tends not to occur with pneumonia and acute myocardial infarction.

QUESTION: What common chemical tests must be done fasting?

ANSWER: a. Serum phosphorus. b. Serum cholesterol.

Edward L. Segal, M.D.*
Martin A. Segal, M.D.*
Ellias N. Manoles, M.D.*
Minneapolis, Minnesota

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*Methodist Hospital, Department of Pathology.

Mammograms

QUESTION: If a mass is palpable in the breast, should a negative mammogram be relied upon as evidence that cancer does not exist?

ANSWER: Mammography is a useful adjunct in the diagnosis of breast carcinoma but it will not take the place of an adequate history and physical examination. Regardless of the interpretation of the mammogram a persistent discrete nodule in the breast should be biopsied and the definitive treatment based on the histopathology. Radical mastectomy should never be performed on the basis of the roentgenologist's report without histological confirmation of cancer.

Biopsies should be performed, however, when the mammogram suggests a lesion, although the nodule cannot be felt. When such a biopsy is taken, the advice of the roentgenologist should be sought to determine the exact location of the lesion. Frequently the lesion is so small relative to the surrounding breast tissue that the tumor can be easily missed. In such cases, a fairly large section of the breast must be removed to be sure of obtaining the right area for diagnosis.

Murray M. Copeland, M.D.
Chairman, Committee on Cancer
American College of Surgeons

To be of true service I must know two things: his need, my capacity. — Panin

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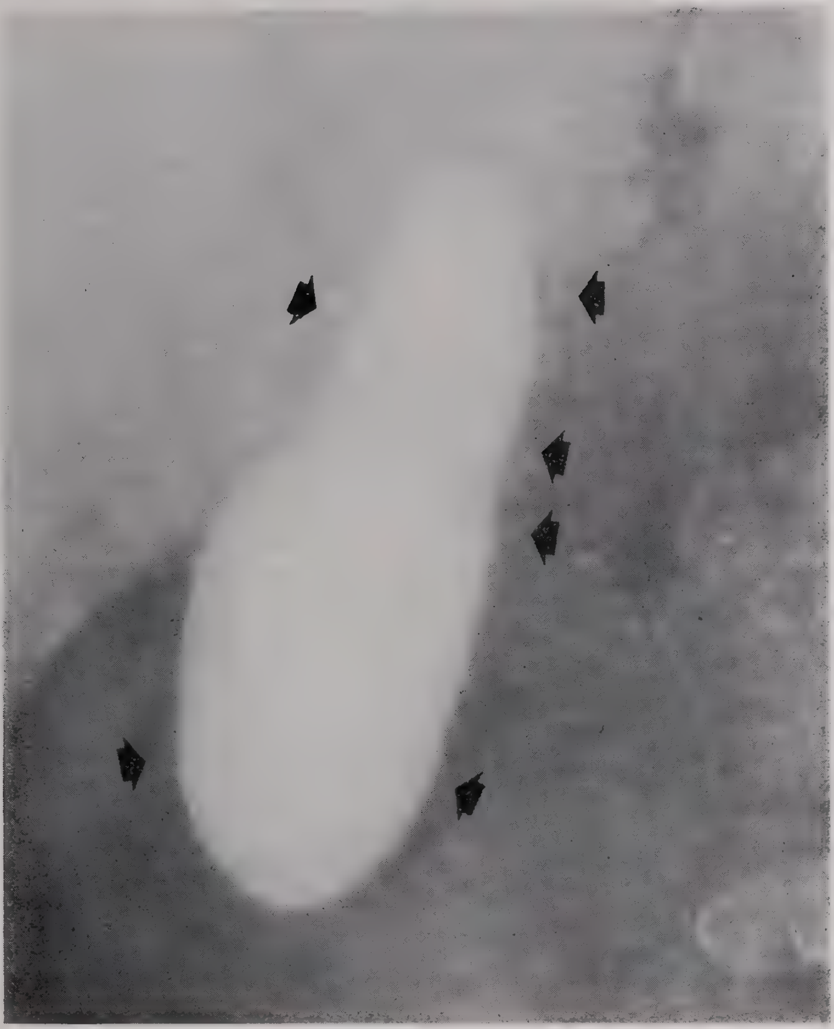
The Viewing Box



A 37-YEAR-OLD, moderately obese, parous, white female presented at The Duluth Clinic with epigastric and right upper quadrant pain of two days duration. The pain was characterized as cramping in nature and was associated with slight nausea. She had a history, during the past four years, of recurrent episodes of mild epigastric and right upper quadrant distress complicated on occasion with intolerance to fatty food. Symptomatology responded with the usual antispasmodics, antacid and dietary programs. There was no weight loss. Abdominal examination was unremarkable; there was no icterus and laboratory studies were within normal limits. It is of particular interest that an oral cholecystogram obtained four years previously, in 1960, revealed excellent concentration of dye, no calculi, but finely serrated margins suggesting the possibility of cholesterosis. An upper G.I. examination and an excretory urogram were unremarkable at the time of the present admission.

The oral cholecystogram routinely includes the post fatty-meal film which reveals multiple sinuses (arrows in Figure 1) extending from the lumen of the fundus into the wall of the gall bladder.

What is your diagnosis?

DIAGNOSIS:

Adenomyomatosis of the gallbladder (intramural diverticulosis)

Adenomyomatosis of the gallbladder is a benign hyperplastic condition involving the epithelium and muscular layer of the gallbladder. There is proliferation with deep branching penetration of the Rokintansky-Aschoff sinuses. Occasionally small papillomatous intraluminal proliferations are also seen. The muscle layer is usually thickened, sometimes grossly, and it is felt that the plexiform arrangement of the muscle bundles facilitates the passage of epithelial expansions. There can be excessive fibrous tissue in the wall.

Radiographic demonstration of dilated sinuses is possible when they are fairly large and other conditions are suitable; e.g., concentration must be good, the neck of the sinuses not occluded and the sinuses not obstructed with stones or bile pigments. These distended sinuses will usually be seen best after the gallbladder has contracted in response to a fatty meal, frequently after one-half hour. However they are sometimes better demonstrated after one or one and one-half hours when the gallbladder has contracted further. We have found laminography, though not essential, very helpful. As in this case, they appear as bead-like structures forming a rim around the gallbladder or they may appear as a cluster at the site of a stricture or of the fundus. Pathologists can aid in confirming the diagnosis if the gallbladder is handled with care at surgery and if the formalin-filled gallbladder is placed in a receptacle containing formalin. This permits the pathologist a greater choice of staining technique.

The condition may be suspected on oral cholecystography when persistent angulation of the gallbladder is found and the wall thickened. Thus, any gallbladder exhibiting strictures, septa, kinks, angular deformities or irregularities of outline should be suspected. Often careful studies of such cases will reveal dilated sinuses. Similarly, gallbladders which concentrate and contract better than usual yet contain calculi should be closely scrutinized.

Frequently symptoms are vague, consisting of epigastric and right hypochondriacal post-prandial discomfort. However, symptomatology may be similar to that of cholecystitis and cholelithiasis. Jutras described three conditions, cholesterosis, adenomyomatosis, and neuromatosis, which frequently co-exist under the term "hyperplastic cholecystosis," and felt that a combination of these conditions would induce excessive gallbladder contraction and hence a hyperfunctional syndrome causing severe lasting pain, intermittent colic and indigestion, biliary dyspepsia and even "psychosomatic" distress.

It seems most likely that adenomyomatosis is essentially a degenerative process associated with aging. It has been pointed out that adenomyomatosis of the gallbladder and diverticulosis of the colon are analogous not only in distribution and morphology of the pockets but also in the intervening structures. To this may be added the fact that both conditions can co-exist in the same individual, a phenomenon that increases with age. However, work with laboratory animals has shown that prolonged administration of estrogens and other steroids may induce fibromyomata of the uteri and adenomyomatosis of the gallbladder. Colquhoun states that this condition is thought to predispose to stone formation and cholecystitis but may be found without either.

It is of interest in this patient that more severe symptoms recurred one year after this study and an oral cholecystogram at that time revealed a thin layer of dense small radiolucent calculi. At surgery the lumen contained innumerable, very minute calculi averaging about one mm. in diameter or less. It is of particular interest that this patient was thought to have hypermenorrhea on the basis of adenomyosis of the corpus uteri, yet another condition morphologically similar to adenomyomatosis of the gallbladder.

Donald E. Dietrich, M.D.*
Duluth, Minnesota

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*Dept. of Radiology, Duluth Clinic.

References

1. Jutras, J. Albert: Hyperplastic Cholecystosis. Amer J Roentgenol 83:795, 1960.
2. Colquhoun, J.: Adenomyomatosis of the Gallbladder. Brit J Radiol 34 #394:101, 1961.

Medical Women on Postage Stamps

Florence Nightingale (1820-1910) was an English war nurse and hospital reformer, who with 37 nurses served in the Crimean War (1854) and who received the Order of Merit (1907). As The Lady with the Lamp she received recognition on postage stamp issues in several countries — among them Belgium (1939), Costa Rica (with Edith Cavell, 1945), Germany (1955), and Nationalist China (1964).

Clara Maas (1879-1901) was a U. S. army nurse who worked with Gorgas combatting yellow fever in Cuba and who, for the cause, allowed herself to be fatally bitten by a mosquito. A Clara Louise Maas and Hospitals postage stamp issued in Cuba in 1951 commemorates her martyrdom.

A Case of Hypo*

"One of the worst cases of hypo recorded was that of an old urine doctor who, feeling bad, set aside a specimen to be examined after it had settled. While he was out of the office a woman who imagined from circumstances that she was in a state of pregnancy decided this would be a good time to find out. She therefore discharged the phial of its contents, and filled it up with her own water. — When the doctor returned (not suspecting any thing of what had transpired), his consternation was inexpressible to find from the appearance of the urine that he was in a state of pregnancy, and realized from the organization and structure of his system that he saw no chance of delivery. He became almost frantic at the discovery, and nothing saved him absolute despair but the discovery of the real facts as they transpired."**

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*Hypo: early 19th century ennui or malaise.

**Pickard and Buley: The Midwest Pioneer, His Ills, Cures, & Doctors. Henry Schuman, New York, p. 69.

If you lend a friend five dollars and you never see him again, it's worth it. — Judge

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Fracture–Trauma Conference

Partially Healed Mandibular Fracture

A 17-YEAR-OLD girl was involved in a two vehicle automobile accident. As a result, she sustained a severe head injury as well as a fracture of the anterior mandible and fractures of the shoulder girdle.

A tracheotomy had been performed shortly after the accident, and she was given general care in her local community. She remained unconscious for about one week and was transferred by a Minneapolis

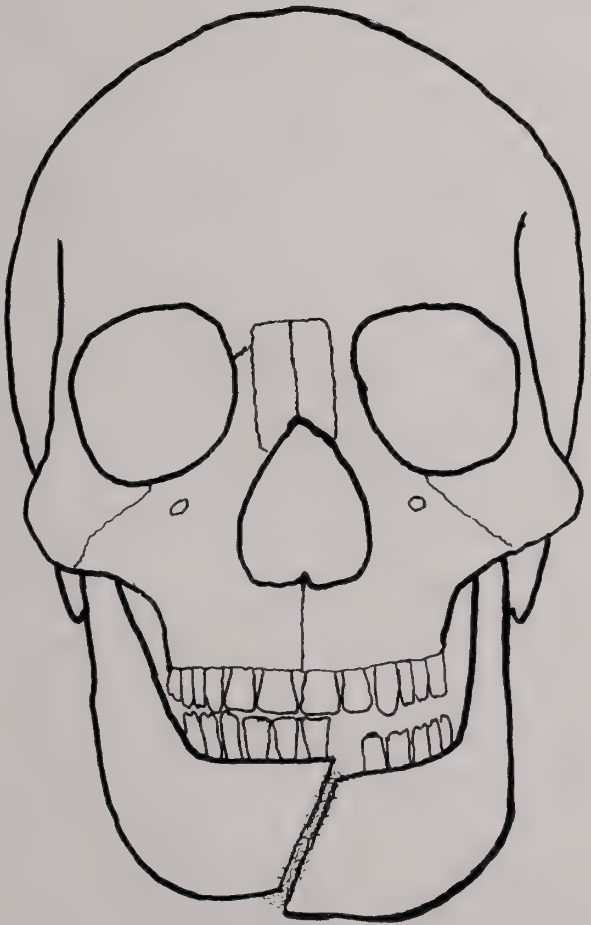

Fig. 1 — Anterior mandibular fracture with displacement of the left fragment about 1 cm. inferiorly. There is nearly firm healing at the fracture site and the patient is unable to close left side of dental arch.

Continued

hospital 19 days after the accident. At this time there was definite malocclusion of the teeth.

Facial Bone Examination

The patient was still not clear mentally. There was an oblique fracture in the anterior mandible with the left fragment overriding the right fragment by about 1 cm. (Figure 1). A palpable deformity was present along the lower border of the mandible, and there was marked malocclusion of the left side of the dental arch. The left mandibular fragment, in addition to being displaced inferiorly, was also rotated lingually. At the fracture site almost complete healing had occurred, so that only slight motion could be elicited. A well functioning tracheotomy tube was in place.

Surgical Correction

Twenty-four days after the accident, the fracture site in the anterior mandible was exposed through an incision at the lower border of the chin. There was considerable callus and fibrous fixation in the fracture site. The area of fibrous union was broken down with a periosteal elevator and the fragments reduced to correct position. Drill holes were placed in the lower mandible (below incisor roots), and the two fragments were held in correct position with a #24 stainless steel ligature through the drill holes (Figure 2). The skin wound was closed in layers.

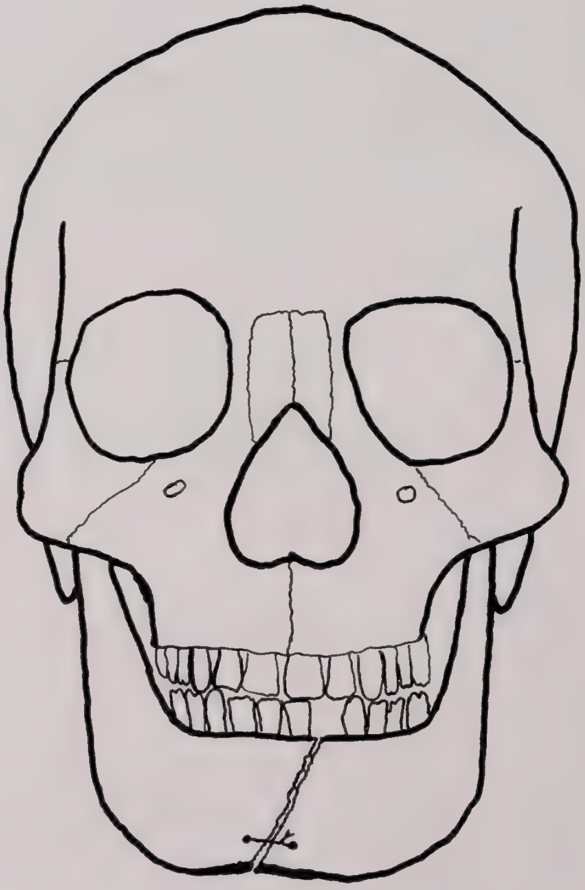

Fig. 2 — Fracture site exposed through incision at the lower border of chin. The area of fibrous union and callus was broken down and the fragments held in corrected position with interosseous stainless steel ligature. Intermaxillary approximation of teeth by use of Erich arch bars and elastic bands was also employed.

Erich arch bars were then ligated to the teeth in the upper jaw and to the teeth in the two lower jaw fragments. The dental arches were held in correct occlusion with elastic bands between the arch bar hooks. The postoperative course was uneventful; dental fixation appliances were removed five weeks later and the jaw was well healed with dental occlusion as before the accident.

Comment

Healing of fractures of facial bones (as in the extremities) in children and adolescents is usually quite rapid. In the case presented, because of the severe head injury, there had been a delay in the management of the mandibular fracture until about three weeks following the accident. Rapid healing in this young person had resulted in nearly firm healing of the fracture but in poor position. Intermaxillary traction alone at this date would not have corrected the deformity.

Reduction of the fragments to normal position was accomplished by breaking down the area of fibrous union and holding the fragments in corrected position with an interosseous wire ligature. Intermaxillary elastic traction with Erich arch bars was also employed. Healing of the jaw in good position with normal occlusion was obtained.

The management of a partially healed mandibular fracture is presented.

Lyle V. Kragh, M.D.
Minneapolis, Minnesota

The Hindu Trimurti

As familiar as Father, Son, and Holy Ghost to a Christian are Brahma, Vishnu, and Siva to a Hindu. This triad consists of Creator, Preserver, and Destroyer. In the operation of cosmic law these three powers are total; Brahma creates the World; Vishnu preserves it as long as it merits preservation; when it inevitably retrogresses, Siva destroys it. But though Siva is the destroyer, he contains within himself the seeds of regeneration for a new and better world — to be created in turn by Brahma, thus completing one cycle and initiating another in the universal evolutionary ascent.

While the esoteric aspects of Hindu cosmogony and cosmology may seem alien to our more materialistic Western minds, we might well ask ourselves in our complacency: Can we Occidentals profit in any way from the Oriental theology? For example, reflecting on the role of Vishnu, are we wise conservers? Under the pressure of 'Progress' are we too fanatically eager to discard the old for the new? Do we repudiate and abandon what still has utility and validity within the framework of our social system? Or, on the other hand, do we make a fetish of the status quo? Do we continue practices and maintain institutions long after they have become obsolete or corrupt?

These are questions that might well give us pause.

Persons who are naturally very fat are apt to die earlier than those who are slender.
— Hippocrates

MOLECULAR REMODELING—

laboratory exercise or clinical necessity?

More than twenty-five years have passed since the discovery of the diuretic activity of sulfanilamide started pharmacologists on a succession of molecular remodelings to find the ideal diuretic.

Diuresis—a sought-after clinical effect from an unwanted side effect

It started in 1937 when a clinician reported that the administration of a sulfonamide was sometimes accompanied by an unexplainable side effect—metabolic acidosis.[1] Three years later the side effect was explained. The sulfonamide radical of sulfanilamide inhibited carbonic anhydrase,[2] the enzyme responsible for converting carbon dioxide and water to hydrogen ions and bicarbonate ions.

Later, other investigators showed by dog experiments that metabolic acidosis probably resulted when the inhibition of carbonic anhydrase upset the exchange of hydrogen and sodium ions, causing increased excretion of sodium as the bicarbonate.[3]

It was twelve long years after the first report of the unexplainable side effect (metabolic acidosis) that it was finally shown that large doses of sulfanilamide administered to edematous patients were indeed capable of promoting diuresis.[4] However, the possibility of toxic effects from its prolonged use and its relatively weak diuretic action made it impractical for clinical use as a diuretic.[5]

Because the inhibition of carbonic anhydrase seemed to be the key to effective diuresis, investigators began to look for more potent enzyme inhibitors —in the hopes that they would be more effective diuretics.

The most important of these early compounds, acetazolamide, enjoyed several years of fairly wide clinical use.

Its carbonic anhydrase inhibitory activity was several hundred times greater than that of sulfanilamide.[6] The increase in inhibitory activity, however, increased not only the excretion of sodium and bicarbonate ions, but also the excretion of potassium.[7] And, like its predecessor, acetazolamide precipitated mild acidosis. Its prolonged use could result in hypokalemic acidosis.[7]

The 'thiazides'—an answer to the metabolic acidosis caused by carbonic anhydrase inhibition

Despite the fact that the sulfonamide group appeared to be responsible for carbonic anhydrase inhibition which in turn appeared to be responsible for diuresis, investigators began to synthesize compounds with structural alterations to the sulfonamide group.

The first major breakthrough came with the synthesis of chlorothiazide. Altering the sulfonamide group did indeed alter the ability of chlorothiazide to inhibit carbonic anhydrase—it was only 1/10th as potent as acetazolamide in inhibiting the enzyme.[8] Despite the drop in inhibitory potency, however, chlorothiazide proved to be an effective diuretic—an observation that led to the conclusion that its diuretic action was due to some mechanism other than its action on carbonic anhydrase.[9, 10]

For effective diuresis, chlorothiazide was administered in daily dosages ranging from 250 to 2000 mg.[11] It increased the excretion of sodium and chloride; and, to a lesser extent, potassium and bicarbonate.[11] The excretion of potassium appeared to be maximal at higher dose levels at which, theoretically, the carbonic anhydrase inhibitory effect is more active.[11] Its prolonged use, therefore, could sometimes result in metabolic hypokalemic, hypochloremic alkalosis.[7]

Naturetin—effective diuresis with more favorable electrolyte balance

Other thiazides followed—with improvements being aimed at two particular areas: 1. attempts to increase diuretic action in relation to the milligram potency of the drug, and 2. attempts at a more favorable sodium/potassium ratio in the urine, i.e., to decrease the excretion of potassium while maintaining the excretion of sodium.[12]

One of these, Naturetin, Squibb Bendroflumethiazide, has made advances on both these points. "By adding a 3-benzyl radical to hydroflumethiazide a rather dramatic reduction in dose range is accomplished. With this drug, effective sodium excretion is obtained with doses between 2.5 and 10 mg., which is a 200 to 1 ratio as compared to chlorothiazide..."[13]

Moreover, due probably to its virtual lack of carbonic anhydrase inhibition, Naturetin (bendroflumethiazide) has been shown to cause less potassium and bicarbonate loss and less alteration in urinary pH than either chlorothiazide or hydrochlorothiazide.

Naturetin is outstandingly effective not only in establishing, but also in maintaining, excretion of retained fluid in edematous patients. And its duration of action is sufficiently prolonged to allow a single daily administration in most patients. Naturetin is also an effective antihypertensive agent.

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Precautions: The dosage of ganglionic blocking agents, veratrum, or hydralazine when used concomitantly must be reduced by at least 50% to avoid orthostatic hypotension. Electrolyte disturbances are possible in cirrhotic or digitalized patients.

Side Effects: Bendroflumethiazide may cause increases in serum uric acid, unmask diabetes, increase glycemia and glycosuria in diabetic patients and may cause hypochloremic alkalosis, hypokalemia; cramps, pruritus, paresthesias, and rashes may occur.

Supplied: Naturetin (Squibb Bendroflumethiazide) 5 mg. and 2.5 mg. tablets. Also available Naturetin c̄ K [Squibb Bendroflumethiazide (5 or 2.5 mg.) with Potassium Chloride (500 mg.)]. For full information, see Product Brief.

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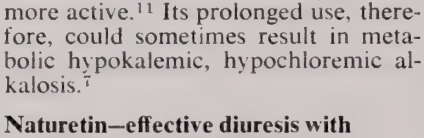

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Tumor Conference

Esthesioneuroblastoma

EIGHTY CASES of esthesioneuroblastoma, or olfactory neuroblastoma, have been reported since the original paper by Berger, Luc and Richard.[1,2]

This neoplasm is seen frequently during the second, third, and fourth decades of life. It has been reported in a child eight years old and, in a few instances, as late as the eighth decade. Males are afflicted more often than females (61%).[3]

The most common symptoms are nasal obstruction and epistaxis, which may be present for months or years. In advanced cases rhinorrea, lacrimation, and frontal headache may be present. Physical examination discloses a polipoid mass in the nasal fossa, but the exact site of origin is difficult to ascertain.[4] Radiological examination shows haziness of the ethmoid and frontal sinuses and in the more advanced cases, cloudiness of the maxillary antrum.

The tumor usually arises from the olfactory mucosa of the upper or middle meatus, middle turbinate, or the roof of the nasal fossa at the level of the olfactory plate.

Microscopically, the tumor is composed of either neurocytes or neuroblasts. Pseudo-rosettes or, less often, true rosettes are seen. Fibrillar component is found in a small number of cases. Histologic pattern and prognosis are not related.

Esthesioneuroblastoma should be differentiated from neuroblastomas arising from the adrenal. The latter are usually in the retroperitoneal space or posterior mediastinal structures but at times metastasize to the orbit and related structures. On the other hand, there is a low incidence of distant metastasis with esthesioneuroblastomas; but their local recurrence rate is high.

No single method of treatment is considered satisfactory. In many instances local recurrence calls for retreatment by the same or other means. A combination of surgery, radiation therapy, and occasionally local fulguration and judicious temporization may be required. Conservative management is usually wise in older patients.

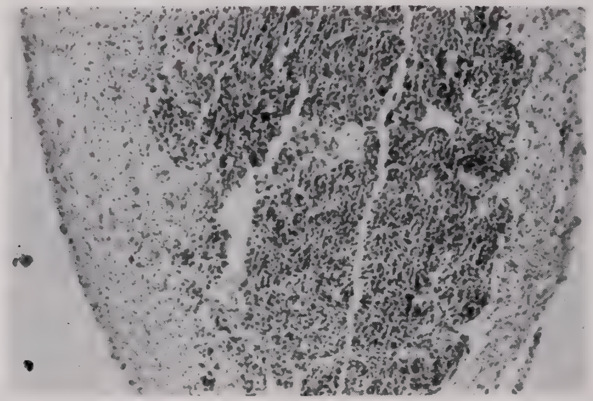
Case History

A 71-year-old white male was seen at the Oncology Hospital of the National Medical Center, Mexico City, Mexico, July 28, 1964. He had had jaundice in 1926 and

Continued

subtotal gastric resection for peptic ulcer in 1931. He gave a history of chronic bilateral otitis media of several years duration. Residual right deafness ensued. In 1945 and in 1961 he had had myocardial infarctions. On admission he said he had experienced left-side nose bleed and a thick, yellow-green discharge for two months. Physical examination disclosed a perforation of the anterior and superior portions of the nasal septum measuring one cm. in diameter and a pink-greyish lobulated mass filling the upper part of the left nasal fossa.

Laboratory tests were normal. Roentgenograms of the paranasal sinuses showed a soft-tissue mass filling the left nasal fossa with partial destruction of the nasal septum and the medial wall of the left maxillary antrum. A biopsy of the mass was reported as esthesioneuroblastoma. Because of the patient's advanced age and his history of heart disease, surgery was not performed. He was given radiation therapy; 5950 rads were administered within an eight-week period. He did well and the mass disappeared.



In April of 1965 his epistaxsis recurred, as shown by a biopsy from the anterior part of the left middle turbinate. Repeat radiation therapy was recommended, and he received 2000 rads from April 22, 1965, to May 8, 1965. At present he is free of symptoms, but a recent biopsy from the same left middle turbinate has shown persistent disease.

Discussion

Neither surgery nor radiation gives a uniformly high cure rate with esthesioneuroblastomas. Either may be used initially or on recurrence. Pathologists may misinterpret the first biopsy and call it an anaplastic epidermoid carcinoma. If the patient survives and has multiple recurrences and an unexpectedly long survival, the disease shows a stubborn tendency to recur locally and may kill by extension to the brain.

Summary

A 71-year-old male, with a two-month history of left-side nasal bleeding and mucopurulent discharge, was found to have an esthesioneuroblastoma. He was treated with two courses of radiation, with a total of 7950 rads being given. He is at present asymptomatic; but a recent biopsy has shown persistent tumor.

Luis G. Krause, M.D.*
Mexico City, Mexico

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*Associate professor of Surgery, University of Mexico, Medical School Chief, Department of Head and Neck, Oncology Hospital, National Medical Center, I.M.S.S. Mexico City, Mexico.

Comment

Dr. Krause's case report brings to mind a moral: rare tumors with confusing names may get lost in dark corners of old medical journals. The problem with the esthesioneuroblastoma is that the esthesioneuroblast, a hypothetical, primordial cell which supposedly arises from the olfactory placode, has never been seen and, indeed, has yet to find its way into medical dictionaries. To compound the semantic difficulties, the esthesioneuroblastoma does not act like a childhood neuroblastoma. It occurs in the older age groups and is an indolent, recurrent growth that kills slowly if it kills at all. Finally, to further muddy the meaning, the esthesioneuroblastoma is purported to arise from olfactory elements (it is sometimes called an olfactory neuroblastoma) ; yet it does not destroy the sense of smell. Because it arises from inside the nose and looks histologically like a neuroblastoma, intranasal neuroblastoma seems a good name.

I suspect that these nuances of nomenclature have piqued the nosological curiosity of more than one physician, and that many esthesioneuroblastomas languish in the files, classified as "atypical, anaplastic carcinomas." Although the original description appeared in France in 1924, an article did not wash into the shoals of the American literature until 1951.[5] As more cases appeared, Mayo clinical physicians caught the scent and, in a retrospective review of their files, came up with eight cases — nearly 10% of those reported to date.[6] Whether one wishes to call the tumor an esthesioneuroblastoma, an olfactory neuroblastoma, or an intranasal neuroblastoma, these facts are clear: the tumor is malignant; it invades locally, recurs after treatment, and is capable of metastases; neither radiation nor surgery is completely effective in checking its growth.

Richard L. Reece, M.D.
Minneapolis, Minnesota

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Derivatively Speaking

Sometimes material dissolved in the bile settles out in little crystals which may collect into hard masses. If these get stuck in the bile duct and form an obstruction, the result is pain and possible surgery. Such masses are called *gallstones* (never "bilestones" since *stone* is from the Anglo-Saxon). On the other hand, the Latin word for a small stone is "calculus" (plural, "calculi") and this name may be used for gallstones. But, because of the change to Latin, they are never called "gall calculi," but always *biliary calculi.*

When gallstones obstruct the way to the intestines, the bile being formed by the liver backs up and is forced into the blood stream. The material in bile consists in part of strongly colored compounds called *bile pigments* (never "gall pigments" because *pigment* is from the Latin "pingere," meaning "to paint").

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Geigy

Neuro-Pediatrics Conference

Battered Child Syndrome*

Dr. A. J. Ellinger:**

This five-month-old white female was brought into my office on February 23, 1965. The mother said that three days before, while the father was babysitting, he propped a bottle of water for the child and went into another room. The father is partially deaf, but he apparently heard the child coughing and choking, went to her, and found that she was not breathing. Mouth-to-mouth resuscitation was given for forty-five minutes. When questioned as to why a physician was not called, the mother stated that no phone was available and that the child responded and apparently seemed well throughout the night. One day prior to being seen, the child began vomiting and continued to do so until she was seen in the office. It was also stated by the mother that the child began to have some twitching of the left arm and left leg, especially after crying a great deal. She was also very irritable. Further questioning of the mother revealed that three or four days prior to the episode of asphyxia, the child had fallen out of a chair about two feet high and struck her head. However, there was no loss of consciousness and she appeared normal.

Past history revealed that the child had a spiral fracture of the right femur on December 16, 1964, which was reported to have occurred when the father was carrying her and her leg struck a door jamb. Dr. McCarthy of the Willmar Clinic cared for her at that time.

The child was born at Fairmont, Minnesota, following a normal pregnancy and delivery. She weighed six pounds, nine and one-half ounces at birth, and no difficulties were noted in the neonatal period. At six weeks of age the child still weighed six pounds, nine and one-half ounces; at four months of age, ten pounds, two ounces. She had received two diptheria-pertussis-tetanus shots and oral polio while living in Fairmont but had had no further medical evaluation since moving to Willmar.

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*Sponsored by the U. S. Public Health Service Grant N2502A63. These conferences are an integral part of the Comprehensive Clinic Program at the University of Minnesota Hospitals. The pediatrics conferences are held every Wednesday from 1:00 to 3:00 p.m. The adult conferences are held every Thursday at 4 p.m. Co-ordinators for the project are Dr. Charles Branthaver and Dr. Edward Defoe in Pediatrics, and Dr. Robert Soll, in Adult Neurology.

Held Wednesday, April 21, 1965 at the University of Minnesota Medical School.

See It's the Law, Page 1359, and Minnesota Med 46:922, 1963.

**Referring Physician, Willmar Clinic, Willmar, Minnesota.

Continued

Physical examination revealed a temperature of 100.6 degrees rectally, head circumference, 39.5 cm., height, 24 inches, and weight, 10 pounds, 6¼ ounces. The child was pallid; no respiratory difficulty was noted. The fontanel was small; there was no tension or bulging noted. The pupils were equal bilaterally and the eye grounds not well visualized. The remaining physical examination was normal with the exception of the neurological tests which showed equivocal extensor toe signs, unsustained bilateral clonus, and brisk reflexes. No spasticity and no convulsive episodes were noted at this time.

The child was admitted to Rice Memorial Hospital for evaluation. She was initially dehydrated, but the electrolytes were normal except for the CO_2 which was 10.2 mEq/L. Urinalysis and white count were normal. The hemoglobin was 10.5 gm.%. X rays of the skull were obtained and showed the sutures to be definitely widened. A bone survey was found to be negative for other fractures except for the healed fracture of the mid-shaft of the right femur.

Subdural taps were performed and definitely bloody fluid was encountered in the right subdural space; the left side was entirely negative. Following the taps there was a moderate amount of leakage of a serosanguinous nature from the right.

A cut-down on the vein was performed and the patient was given one-third normal saline. While she was in the hospital, definite Jacksonian type convulsive movements were noted in the left extremities, and there was a slight paresis of the left side with some spasticity. The child was referred to the University Hospitals for further evaluation.

Dr. Burton Dudding:* Upon arrival at University Hospital, the child was alert and responsive. On review of system history it was learned that the child did bruise easily with spanking, and these bruises lasted two to three days over the buttock region. There was no family history of any bleeding disorder. Social history will be given later in the discussion.

Physical examination at the time of admission showed a small, poorly nourished white female with an active intravenous infusion attached. The skull was asymmetrical with a bulge on the right side. Funduscopic examination showed diffuse bilateral preretinal hemorrhages and vitreous hemorrhage on the right. Fullness of the right thigh was noted, as well as weakness of the left arm and leg. The weight was 5.2 kg., which is below the 10th percentile; the length was in the 50th percentile. Neurological examination showed a slight ptosis of the left eyelid and a slightly drooping angle of the mouth on the left. The patient would not reach for objects with the left hand, which was slightly flaccid and lying at the side. Muscle tone was definitely decreased in the left arm and left hand. On the right the patient had a good grasp reflex, not obtainable on the left. There was no evidence of spasticity or scissoring; the extensor tone in the lower extremities was good.

Laboratory studies showed a normal white count and urinalysis. The hemoglobin was 9.6 gm.%. A bleeding workup revealed a normal partial thromboplastin time, prothrombin time and platelets. Roentgenograms showed not only the healing fracture of the right femoral shaft, but periosteal new bone formation of the shaft of the left femur. No other evidence of trauma was present.

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*Pediatric Intern, University of Minnesota Hospitals.

A repeat subdural tap was performed and approximately 1 cubic centimeter of bloody fluid was obtained from the right side; none was obtained from the left. The patient tolerated these procedures well. Eight days after admission another repeat right subdural tap was performed and no fluid obtained.

An electroencephalogram was compatible with a subdural on the right side. During the first two weeks of hospitalization the patient continued to vomit intermittently; consequently the caloric intake was less than expected. By the end of the second week she was taking 120 calories per kilogram and beginning to recover muscle function of the left side. On discharge, March 21, 1965, she had gained weight satisfactorily, and during the previous two weeks had shown signs of rapid clinical improvement from the neurological standpoint.

Initial impression was that this child presented an instance of the Battered Child syndrome by virtue of the following reasons:

1. The patient had a history of apnea which required resuscitation with mouth-to-mouth breathing by the father for forty-five minutes; but no medical attention was sought by the parents after this episode.
2. There was insufficient historical data to account for either the subdural hematoma or the bilateral preretinal hemorrhages.
3. There was a past history of fracture of the right femur, again with little historical data to account for this fracture as entirely accidental; also the skeletal survey showed evidence of residual periosteal hemorrhage of the left femur.

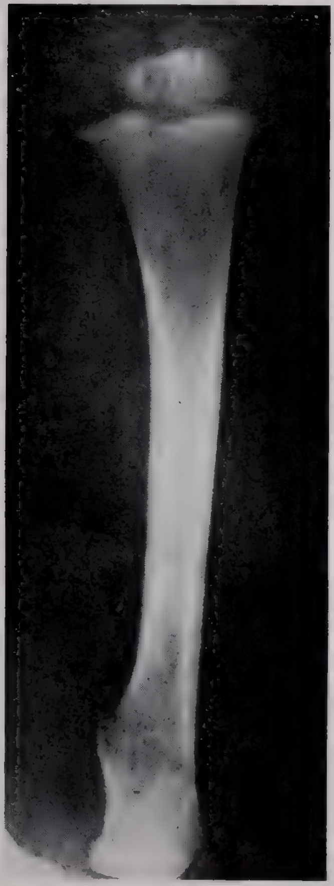

Fig. 1 — Roentogenogram of left femur showing periosteal new bone formation which is associated with trauma.

Continued

4. The mother admitted that the child bruised easily when she spanked her for crying.

5. The patient's weight gain was poor in contrast to normal growth in length, and no metabolic or other basis could be found to explain the findings.

6. The family and social history were compatible with the diagnosis of Battered Child syndrome, since surveys have revealed that over 50-90% of children who show the effects of this syndrome are the products of unwanted pregnancies and of serious social problems.[1,2]

Miss Helen Kretchmer:* Once the diagnosis of Battered Child syndrome was established, the philosophy was to help these parents as much as possible and not to instigate punitive procedures. The protocol used by the University Hospital was a telephone call to Mrs. Nelson, the social caseworker in Willmar, as well as a report from the hospital administration to the police in Willmar. These calls were followed by a letter regarding the total situation.

The father, aged 21, is currently in his first year of a two-year college course studying to be a draftsman under the Vocational Rehabilitation program. This support consists of tuition, books, and $20 a week for living expenses. He has a 75% bilateral congenital hearing loss and wears a hearing aid. He plans to take a job in June, 1965, in St. Cloud, Minnesota. The mother, aged 18, left high school in her junior year because of this pregnancy. Because of serious financial problems she is currently working as a waitress in a local cafe from four p.m. to midnight four days a week. The parents were married March 26, 1964, and the patient was born October 1, 1964. Both grandparents apparently did not favor the marriage but did support it. According to the mother, the father's side of the family represents an unstable situation; his nine-year-old sister has had a nervous breakdown apparently precipitated by the father's activities with other women. The mother's family is relatively stable. The young mother expressed her wish to finish high school and at one time wanted to become a neurosurgeon. She read a great deal and acquired no familiarity or experience with child-rearing practices.

When the parents established their home in Willmar after the birth of the baby, they had many adjustments to make. The baby slept in the same room with the parents, and she seemed to cry excessively. The mother became very irritated at the baby's crying, especially in the morning after she had worked the previous evening. She admits that this crying often caused her to lose her temper and spank the baby. The father, on the other hand, does not seem to be too disturbed by the child since he can shut off his hearing aid. The ideas expressed by both parents on child rearing are both inconsistent and immature.

When this child was discharged from the hospital she was placed in the care of the maternal grandparents; but no action has been taken for legal custody either by the maternal grandparents or by Martin County.

Dr. Harold Ireton**

A screening evaluation of the child's intellectual functioning by the Cattell Infant Intelligence Scale was made. On the basis of this test the child seemed to be functioning with approximate consistency for her age.

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*Medical Social Worker, University of Minnesota Hospitals.

**Clinical Psychologist, University of Minnesota Hospitals.

In view of the history one would be somewhat hesitant to make any prognosis at this time; certainly she should be re-evaluated, preferably at age two, unless there is evidence of obvious developmental defects prior to this time.

The Parents

Both parents presented as friendly and cooperative, although the mother appeared somewhat superficial in her emotional expression, and the father appeared somewhat tense. Although they both admitted that they had been somewhat harsh in the way they handled their child, they supported each other's contentions that they had not been extreme in their handling. The mother reported that the child deserved the spankings that she got and the father added, "You have to do something to shut her up." In describing the episode preceding the child's hospitalization, the father stated that he slapped her "because she wouldn't stop crying. I was under pressure . . . a final test coming up . . . she fought me, cried . . . I slapped her." The mother reported that her spankings may have "bruised her a little bit." Regarding their marriage, both deny major problems; however, they admit that they had to get married. The impression is gained that there are significant husband-wife conflicts which both parents minimize or deny.

The Mother

The mother's history also includes a suicide attempt at age 13 with aspirin "because my brother picked on me." From the interview material the mother attempts to present herself as intelligent, mature, and interested in the welfare of her child. Basically, however, she appears quite immature, manipulative, and unwilling to accept adult responsibility. She appears rather self-centered and probably is quite emotionally detached from the needs of others.

The Father

The father is somewhat tense and on the defensive, although he did communicate considerable information. Personality testing tended primarily to reflect this defensiveness, although it did point to features of anxiety and emotional instability. In the interview he stated that everyone in his family had always been nervous and touchy. He is apparently doing well in school but acknowledges considerable tension in connection with multiple responsibilities of finance, family and school. By history, he has suffered numerous handicaps to normal development. Physical problems have included tunnel vision, hearing deficit, and an associated speech problem. He reports that he could not say his own name until junior high school when he was provided with a hearing aid. He could not live up to his father's ambition that he be a boxer like himself and fell primarily under the social influence of his mother and sisters. This pattern of physical and social disabilities has apparently left him quite insecure in his masculine identity, although he does not directly acknowledge this; however, a paranoid sensitivity is subtly indicated. Consistent with this, following an auto accident four years ago, he was apparently confused and suspected that everything was poisoned.

Both parents appear limited in their ability to provide for their daughter emotionally, but for different reasons. The mother appears to be psychopathic in her emotional detachment from the needs of others, while the

Continued

father is quite insecure, sensitive, and wrapped up in the struggle to maintain his defenses against his own insecurity and anxiety. This situation would suggest an unfortunate future for this marriage unless changes can be made.

As far as recommendations are concerned, it is essential that the parents receive psychological counseling. This should be provided locally in Willmar through the mental health center.

Dr. Kenneth Swaiman:* The condition we are discussing today is certainly not new, but it is only recently that physicians have recognized the connection between subdural hematomas and multiple long-bone fractures.[3,4] Caffey[3] originally thought this complex was due to a metabolic disease. The primary implications of the Battered Child syndrome are that a great majority of these children die from brain trauma or have serious sequelae; the bones heal but the brain does not. This patient demonstrated some of the immediate signs one notes in the diagnosis of a subdural hematoma: seizures which are not necessarily focal in nature and loss of contact with the environment. The small volume of the subdural hematoma does not explain the entire clinical picture. One must assume that there was brain contusion which probably consisted of intracerebral hemorrhage and edema. The electroencephalogram revealed slowed fast activity and slow-wave foci compatible with subdural hematoma as well as with underlying brain damage. However, the usual prognosis of a subdural hematoma may not be applicable to this child. Usually, in infants, cranial sutures are not rigid and tend to spread; thus there is room for expansion of the underlying pressure. From history, one can not be sure whether this child has had more episodes of cerebral damage.

This child did show improvement in the left hemiparesis, which indicates some resolution of the right-sided injury of the brain. In the future, speech problems are less likely to occur, because 99% of the people who are right-handed have the speech center on the left; and of those who are left-handed, 90% have the speech center on the left. We have no guarantee that this child may or may not have seizures in the future. She should be maintained on small doses of phenobarbital for the next year.

I would agree with Dr. Ireton in being skeptical of her future development, judging solely on the basis of her motor ability at this time. In regard to management of her subdural hematomas I doubt whether there would be any need for surgery, and we will follow this child by periodic skull transillumination and head measurements. Electroencephalography may not be as helpful, as the changes seen may be permanent.

Dr. Dudding: When this child was discharged from the hospital, she was released to the care of the maternal grandparents, and legal custody has not been insured. When she was last seen, she was gaining weight and seemed to be making an excellent recovery.

Mrs. Lucille Nelson:** This family's initial contact with the Willmar Welfare Department was as a transient couple in financial need for medical care. They seemed to be very immature in their ability to care for their baby, and she was very difficult for them to accept. Following the hospitalization of their child the parents returned to their home. Unfortunately, the police, when they were notified of a possible battered child, did not in turn notify the welfare department as to their course of action, but took it upon themselves to interrogate the parents and were apparently a "little rough." The sheriff later apologized for this. I was somewhat hesitant in approaching the family as I felt that there might be resistance as a result of the police interrogation. However, at the time of the interview the father seemed quite relieved, and both parents appeared to be seeking support. Both expressed the wish that their child would soon be returned to them; however, their routine seemed to be "better now since the child was not in the home."

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*Assistant Professor, Pediatrics and Neurology, University of Minnesota Medical School.

**Child Welfare Social Worker, Kandiyohi County.

During a second visit with the parents they were encouraged to attend the West Central Mental Health Center for evaluation. This was done, and a staffing conference was held. In general, conclusions were that the child should be maintained in the maternal grandparents' home until this couple has been settled in their new home and show definite evidence that they have some realization of their responsibilities, while making consistent efforts to improve.

Mrs. Mary Jean Campbell:* I would certainly recommend that cooperation and good communication between the various communities involved be stressed. This can be done on an inter-county basis by maintaining continuity of communication, when this family moves to St. Cloud. As this child is presently with the grandparents in Iowa, I strongly feel that the University Hospitals should maintain the primary medical responsibility until this family is settled in St. Cloud. Also legal custody by Martin County should be obtained to prevent the child from being returned to the present home situation.

Dr. Robert ten Bensel:** Mrs. Campbell's points are well taken. It is extremely important that legal custody be taken of the child to insure that she does not re-enter the home until the family is under casework services. DeFrancis[5] points out that physical abuse will continue if children are returned to a home where the personality disorders of the parents go untreated. Repeated physical abuse has reoccurred in as many as 40% of such cases. The incidence of death in these cases in unknown.

The situation described by Mrs. Nelson merits some comment. A revision of the Minnesota Battered Child Law is presently before the state legislature and will insure the dual reporting and cooperation of the police and county welfare departments in these cases.†

Final Recommendations of the Conference:

1. Since the child is presently with the maternal grandparents in Iowa, the University Hospitals will maintain medical responsibility until this family has made the move to St. Cloud and a final disposition is made through the mental health center and county welfare department.

2. Medically, this child needs to be maintained on phenobarbital for the next year as a prevention against seizures. Secondly, she should be reevaluated psychologically at two years of age for possible residual damage. Careful observation should be maintained to determine whether the subdural reaccumulates.

3. We cannot over-emphasize restorative measures for the family. Every

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*Director, Martin County Welfare Board, Fairmont, Minnesota.

**Moderator.

†Minnesota Statutes 1961, Section 626.52, Sec. 2. See page 1359.

Continued

possible attempt should be made within the community to insure that the parents realize their responsibilities and make efforts to assume them. However, from the above discussion this will be a difficult task in view of the psychopathology of the parents.

4. Legal custody of the child by Martin County is recommended until the family situation is resolved and a legal decision is made regarding the advisability of returning this child to her home or placing her permanently elsewhere.

5. Inter-county communications should be maintained as to progress with the family. Communications to the University Hospitals should be made to Dr. Dudding or Dr. Swaiman.

Robert W. ten Bensel, M.D.*
Conference Moderator

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*Presently in the Service of the Armed Forces.

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The Stethoscope Discovered

Laennec* had under his care an exceedingly stout woman suffering from heart disease. Listen as he might, he could not hear the heart sounds clearly. On his way to visit this patient, Laennec was passing through the courtyard of the Louvre. A heap of old timber was lying in one corner, and some children were playing there. They had discovered a new game. One of the pieces of wood was a long beam. A youngster had his ear at one end of it, and another was signalling by tapping the other end. This gave Laennec an idea. He quickened his steps, and, when he reached his patient asked for a quire of letter-paper. Having rolled this paper into a cylinder, he applied one end of it to the site of the cardiac impulse and listened at the other end. The result was marvelous. He could hear the heart-sounds much better, much more plainly, than with his ear on the chest. Moving his paper cylinder from place to place, he listened to the sounds that were forthcoming all over the heart. Then he listened to the breath-sounds. They were so loud that they startled him. The stethoscope had been discovered, the auditory tube which was to become symbolical of latter-day physicians as the urine-glass was of the medieval doctor.**

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*Laennec (1781-1826) was a French physician.
**Massengill, S. E.: Sketch of Medicine and Pharmacy. S. E. Massengill Co., Bristol, Tenn-Va., p. 102.

The disease of an evil conscience is beyond the practice of all the physicians of all the countries in the world. — Gladstone

Medical Seminar

Diagnosis and Treatment of Regional Enteritis

Presented as a Seminar

Sponsored by

The Faculty of the Mayo Graduate School of Medicine

REGIONAL ENTERITIS is a granulomatous disease of the gastrointestinal tract, which has been reported to occur anywhere from the esophagus to the anus but which most frequently affects the last 12 inches of the ileum.[1,2] It is characterized pathologically by noncaseating granulomata and by thickening of all layers of the intestinal wall and its mesentery. Clinically it is associated with a long course, punctuated by remissions and exacerbations. Our ignorance about its etiology remains almost as complete now as it was in 1769, when the disease was first described.[3]

Primarily a disease of young people, regional enteritis can occur at any age. In 40% of cases it affects persons aged 21 to 30 years and, in 85%, those aged 10 to 40 years. The sexes are almost equally afflicted, but male patients are slightly more commonly represented in most series. There seems to be little racial predilection,[1,3] although some authors have found a higher incidence in members of the Jewish race.[4]

Classification

We can classify this disease into four major categories, recognizing that overlapping of one category into another does occur: (1) acute regional ileitis, (2) ileojejunitis, (3) regional enteritis affecting the colon, and (4) chronic regional enteritis (most common type). Regional enteritis involving the esophagus, stomach, or duodenum is quite rare and will not be discussed.

Acute Regional Ileitis

Acute regional ileitis[1] presents with a clinical picture nearly indistinguishable from that of acute appendicitis. The patient has the acute onset of crampy abdominal pain, tenderness in the right lower quadrant of the abdomen, and mild fever. Frequently a lower-abdominal mass may be felt. At operation, the findings of a congested, boggy ileum, heavily matted onto nearby intestine, and of enlarged mesenteric lymph nodes allow the surgeon to make the diagnosis of acute regional ileitis. This is essentially an operative diagnosis, for clinical differentiation from appendicitis is quite difficult. The only possible differentiating point is that in acute regional ileitis there is the onset of diarrhea at the same time as the pain begins. This is unusual in appendicitis, where the patient is usually constipated. Since exceptions to this rule do occur, operation is almost mandatory.

If there is no history of chronic diarrhea antedating the acute episode, the prognosis is quite good; there is then a 50% to 90% chance that the patient will recover completely.[5,6] Chronic diarrhea, existing prior to the acute episode, is thought to indicate a preexisting chronic regional enteritis.

Ileojejunitis

Ileojejunitis may be defined[1] as that form of chronic enteritis in which the granulom-

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atous process typical of that disease involves the jejunum, either as an extension from the ileum, or as an independent lesion limited to parts of the upper portion of the small bowel. Ileojejunitis resembles regional enteritis closely in clinical manifestations, except that malabsorption and malnutrition are more common in the former. In general, its clinical course is more benign than that of classic regional enteritis; however, because it often involves large segments of bowel, it is also less amenable to surgical correction.

Regional Enteritis Affecting the Colon

It is now thought by leading authorities[7] that this clinical and pathologic entity is separate from chronic ulcerative colitis. The differential points relate mainly to differences in distribution and appearance of the local lesions. The rectum is involved in 95% of cases of ulcerative colitis but in only 50% of cases of colonic regional enteritis. On the other hand, anal lesions are much more common in regional enteritis affecting the colon, occurring in about 80% of persons having this disease. The most characteristic lesion here is a perianal ulcer; this is indolent-appearing, undermined, and quite chronic. In some clinicians' hands, biopsy of this lesion will show noncaseating granulomata in 85% of cases.[7]

Further, in the roentgenologic examination of patients having regional enteritis of the colon, one will see only sporadic involvement, with islands of normal-appearing mucosa interspersed among areas of deep ulceration, which give diseased segments of colon a "feathered" appearance. In ulcerative colitis the colon is usually more diffusely involved, and the ulcers which one sees are quite shallow. Further, internal fistulae between the colon and other organs are rare in ulcerative colitis but relatively common in regional enteritis of the colon.

In this disease, proctoscopic examination may show typical deep linear ulcerations; the mucosa may be swollen, giving it a cobblestone appearance. In contrast, in ulcerative colitis, proctoscopy reveals broad, flat, superficial ulcers; and the mucosa is granular and friable, bleeding easily. Thus the patient having ulcerative colitis usually has gross blood in his stools; whereas the patient with regional enteritis of the colon rarely has.

Finally, persons having regional enteritis of the colon are very seldom seriously systemically ill ("toxic") from their disease. In fact, to date, no case has been reported of acute toxic megacolon in regional enteritis.[8] This is, of course, very different from what occurs in chronic ulcerative colitis. However, it should be stressed that in some few cases there is no way of telling whether a patient has chronic ulcerative colitis or regional enteritis, even when the operative specimen is in the pathologist's hands.

Chronic Regional Enteritis

This is the common form of the disease and will be the subject of the remainder of this paper. Here the terminal 12 inches of the ileum are involved primarily.

Burril Crohn, whose paper in 1932 brought regional enteritis to the attention of the medical profession, maintained[1] that "the diagnosis is essentially a clinical one, based upon the characteristic subjective symptoms and the physical findings." While we have all seen or heard of cases of regional enteritis in which no one could have made the diagnosis clinically, certainly we can be suspicious of regional enteritis in appropriate cases, if we learn the characteristic clinical picture.

Clinical Findings

Common Symptoms and Signs

The most common symptoms and signs of regional enteritis are shown in Table 1. (Percentages are based on 1,342 cases reported in four series.)[1,3,9,10]

Abdominal Pain. — The pain is usually colicky and localized in the lower part of

TABLE I
Symptoms and Signs of Regional Enteritis

Symptoms	Cases, %	Signs	Cases, %
Abdominal pain	93	Fistulae	52
Diarrhea	84	Mass	32
Loss of weight	41	Anemia	20
Fever	36		

the abdomen, frequently in the right lower quadrant. It is often preceded by eating and is relieved by defecation or the passage of flatus. This is the characteristic predefecation pain of regional enteritis. It is probably caused by partial obstruction of the small bowel.

However, there is another kind of pain which a patient with regional enteritis may experience. This is a steady dull pain, usually in the right lower quadrant, not relieved by defecation. Often a sign of abscess or fistula formation, this pain occurs late in the course of the disease.

Diarrhea. — This symptom also has certain distinctive clinical features. Following the general rule that diarrhea decreases in intensity the farther away the lesion is from the anal sphincter, in the usual case of regional ileitis diarrhea is moderate. The patient may have two to five stools per day. The stools are soft and mushy and may contain just a bit of mucus but no pus. Gross blood in the stool is rare; indeed, the guaiac test for blood in the stool may give negative results in cases of regional enteritis. Occasionally, in about 5% of cases, the patient is constipated.[1]

Loss of Weight. — Loss of weight averages 10 to 20 pounds but may be much greater. In far-advanced cases the patient may look as cachectic as someone with terminal carcinoma. The mechanisms in operation here include the patient's aversion to food (since eating aggravates the pain), malabsorption, intestinal hurry, and internal fistulae.

Fever. — Fever occurs mostly during the inflammatory stages of the disease; it is usually absent in remission or in the late, cicatrizing stages. The fever is usually low-grade and not accompanied by chills. However, if the fever is high and runs a septic course, then one must suspect the occurrence of an intra-abdominal fistula, abscess, or perforation. If the pain and diarrhea are mild but fever is prominent, regional enteritis may present as "fever of unknown origin."

Abdominal Mass. — In this disease, such a mass is usually found in the right lower quadrant of the abdomen and consists of an abscess or of inflamed adherent loops of bowel, often interconnected by fistulous tracts. The size of the mass varies; it may have the diameter of a 50-cent piece or may be larger than an orange. On occasion, it may be felt only on vaginal or rectal examination.

Anemia. — The anemia that is present in about 20% of cases consists, for our purposes, of a hemoglobin value of less than 11 gm/100 ml. of blood. The mechanisms involved in the production of this anemia include chronic blood loss, malabsorption of iron and other substances, and the occasional blind-loop syndrome.

Fistulae. — Three types of fistulae occur in regional enteritis: internal (41%), external (22%), and perirectal (38%).

Internal Fistulae (41%) — In almost all cases, these originate in the diseased terminal ileum and communicate most commonly with the cecum and more proximal portions of the ileum, but fistulae have extended to the sigmoid colon, urinary bladder, vagina, fallopian tubes, urethra, and so on. These are usually seen easily on roentgenograms and are quite characteristic of regional enteritis. The precursors of these fistulae are probably the deep linear ulcers seen in diseased portions of intestine.

External Fistulae (22%) — These ordinarily open onto the anterior abdominal wall and practically never occur without an antecedent abdominal operation, usually an appendectomy. The sequence of events is much like this: the patient has an operation, and the incision heals well at first; however, within five weeks the incision breaks down and a small fistula appears, which may persist for months or years. The fistula may not be apparent until years have gone by, but in more than 75% of cases, it will be seen within five weeks.[1] It usually exits at the incisional site, but the external opening may on occasion be seen anywhere in the abdomen-inguinal region, psoas region, and so on. It has been postulated that when the surgeon breaks down adhesions with his exploring hand, he may enter

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an abscess cavity, which then breaks out through the traumatized abdominal wall.

Perirectal Fistulae (38%) — These occur in more than 20% of cases of regional enteritis, if we include rectovaginal fistulae.[11] Interestingly enough, they may antedate the abdominal symptoms of the disease by years. In one series,[11] rectal complaints predated the diagnosis of regional enteritis by at least one year in 29% of all cases of regional enteritis seen at the institution where the study was made.

Uncommon Signs and Symptoms

Less common manifestations of regional enteritis include arthritis (3% to 8%), clubbing (3% to 4%), ocular difficulties (5%), erythema nodosum (1% to 2%), and splenomegaly (1%). The arthritis may be rheumatoid-like or like ankylosing spondylitis. The severity of the arthritis parallels closely the activity of the intestinal disease, often disappearing during a remission. In no case is there a positive rheumatoid flocculation.[10] The clubbing is indistinguishable from that which occurs in pulmonary disease and is important only for that reason. We must remember that regional enteritis causes clubbing and not subject a patient with regional enteritis and clubbing to a lot of unnecessary pulmonary tests. The eye problems seen are quite varied; iritis and iridocyclitis are the most common, but keratitis, corneal ulcers, episcleritis, and phlyctenular conjunctivitis have all been described.

Proctoscopic Findings — There are, all in all, six proctoscopic clues to the diagnosis of this illness.[11] Proctoscopic examination may reveal one or more of the following: (1) anorectal abscesses and fistulae, (2) indolent anal or perianal ulceration, (3) extrarectal or intra-abdominal masses, (4) deep, linear ulcers of the mucosa, (5) cobblestone appearance of the mucosa, and (6) granulomas of the rectum or sigmoid colon.

We have already mentioned most of these clues in discussing regional enteritis of the colon. Suffice it to say that the frequency of all these signs is greatest when colon and rectum are involved, as might be expected. In summation, suppurative perianal fistulae in the presence of diarrhea indicate a pathologic inflammatory process somewhere in the intestine. Most commonly this will prove to be regional enteritis, ulcerative colitis, or tuberculosis of the small intestine.

Roentgenologic Findings — When one clinically suspects regional enteritis, one usually seeks confirmation of his clinical impression through gastrointestinal roentgenograms. Since the terminal ileum is involved in more than 90% of cases,[12] often a colon examination will suffice for the initial examination. A practical point here is that we can do a roentgenographic study of the colon even in the presence of subacute obstruction, when small-bowel roentgenography would be contraindicated. Further, this provides us with yet another way of ruling out ulcerative colitis.

The radiologic appearance has been divided, rather arbitrarily, into stenotic and nonstenotic phases, depending on whether or not irreversible fibrosis has occurred.[13] The earliest sign in the nonstenotic phase is caused by submucosal edema and consists in flattening, blunting, and thickening of the valvulae conniventes. The bowel lumen may become irregular. Then longitudinal streaks of barium are seen, representing shallow ulcers; this causes the characteristic cobblestone appearance, best seen in the proximal portions of the intestine. Soon the ulcers become deeper, giving the intestine a feathered appearance. Occasionally, small inflammatory polyps may be seen. Fistulae to other organs may also be seen.

In the stenotic phase, all of the above may be seen; but added to these is the dilatation of the bowel just proximal to the lesion. Fluoroscopically, the stenotic bowel is never seen to fill out with barium.

The famous string sign of Kantor is usually seen in the terminal ileum. It is a thin shadow, said to look much like a frayed cotton string. This sign does not always mean that irreversible stenosis has occurred, for it also may be caused by edema and spasm in the nonstenotic phase of the disease. This string sign is quite suggestive of regional enteritis; indeed, it is present in about one third of cases.[12] However, it is important to remember that other diseases may also present with this sign—for example, actinomycosis and tuberculosis of the small bowel and carcinoid involving the terminal ileum.[1]

Differential Diagnosis

In a recent review, Eisenstadt[14] listed more than 70 different diseases in considering the differential diagnosis of regional enteritis. As space is lacking to discuss all of these, I shall elaborate on only a few interesting diseases with which this disease may be confused (Table 2).

TABLE 2
Some Diseases Which May Be Confused With Regional Enteritis

Ulcerative colitis
Tuberculosis of the small bowel
Mesenteric arterial insufficiency
Carcinoid of the terminal ileum
Irritable bowel syndrome

Ulcerative Colitis

I have already discussed most of the differential points between ulcerative colitis and regional enteritis; the most characteristic differences are seen in the roentgenographic and proctoscopic examinations.

Tuberculosis

Tuberculosis of the small bowel can mimic regional enteritis quite well, a fact of special importance in areas where tuberculosis is endemic. The key feature to remember about tuberculosis of the small bowel is that it almost always co-exists with pulmonary tuberculosis — in this country, at least.[7] Thus a roentgenogram of the chest and a tuberculin test are of special significance. However, the final distinction between tuberculosis of the small bowel and regional enteritis may not be made until the operative specimen is in the pathologist's hands. Caseation or evidence of acid-fast bacilli on tissue examination or culture will then provide proof that the lesion is of tuberculous origin.[14]

Mesenteric Arterial Insufficiency

Chronic mesenteric arterial insufficiency is receiving increasing attention as a clinical entity diagnosable before death. It is not hard to visualize how partial ischemia of a segment of intestine could lead first to inflammation and then to healing, with fibrosis and scarring. This could then, if it involved the terminal ileum, give a small-bowel roentgenographic picture resembling that of regional enteritis. However, mesenteric arterial insufficiency usually occurs in older persons who have evidence of arteriosclerosis elsewhere. These persons have "intestinal angina," in which pain of a crampy nature occurs within 30 minutes after eating. It may be generalized or periumbilical and is often quite severe. However, it is not usually relieved by the passage of stool or flatus, as is the pain of regional enteritis; indeed, it may be resistant to standard medications for pain. The only consistent pain relief occurs when the individual avoids food. Pain is the most predominant symptom here, far more so than the diarrhea which may occur. Diagnosis is important, because surgical treatment is available and may be most helpful. Properly performed angiography of the mesenteric vessels remains the only method of definitive diagnosis short of surgery.[15]

Carcinoid Tumors

Carcinoid tumors of the ileum are rare but deserve mention. Because of their chronicity they may be present for many years, mimicking regional enteritis very well, especially if the full-blown carcinoid syndrome is not present. However, if the patient has severe, persistent flushing or pulmonary or tricuspid murmurs, then it would seem prudent to obtain a urine collection for 5-hydroxyindolacetic acid. If the terminal ileum is not involved in a case suspected of being regional enteritis, then one should be suspicious of carcinoid. However, it is rare for this diagnosis to be made preoperatively.[16]

Irritable Bowel

Finally, one should not forget the ever-present irritable bowel syndrome. This can cause diarrhea, abdominal pain, and, on occasion, mild loss of weight. However, one

Continued

never sees an abdominal mass, fever, or internal fistulae as a part of this syndrome.

In the classic case of regional enteritis, clinical and laboratory studies will confirm the diagnosis with something approaching 99% certainty; the only way to achieve 100% certainty is to confirm the diagnosis at operation.

Treatment

Since this is, in general, a disease characterized by spontaneous remissions which may last for years, it has been exceedingly difficult to evaluate conservative therapy in any objective manner. There have been few double-blind, controlled studies carried out to point scientifically to the most advantageous forms of therapy. Treatment of this disease, therefore, remains to a large extent empirical. Most of the measures which have been advocated include: diet and dietary supplements; rest; the administration of anticholinergics, sulfonamides, antibiotics, adrenal steroids, and nitrogen mustard; irradiation; and operation.

Diet and Dietary Supplements

Different clinicians vary in the severity of the diet they impose on their patients; but in general all agree that the diet should be high in calories, carbohydrate, and protein and at least mildly restricted in residue. It has been suggested that eating five small meals a day might be a good plan, especially for patients who find that eating increases their pain. In the past there has been considerable comment about milk allergy in this disease.[3] However, this is now thought not to be of major importance, and milk is not specifically forbidden unless the patient notes that it causes an increase in his symptoms.

Protein supplementation with a drink containing Gevral protein or a similar preparation may be indicated. Vitamin supplements also are used — B complex, and vitamins A and D. Anemia may call for the use of parenteral or oral iron or for injections of vitamin B_{12}, depending on its cause. If calcium or potassium are lost in sufficient quantity, they also may need replacement. Each case must be considered individually and treated accordingly.

Rest

As in any chronic illness, rest may be very important. However, the patient need not be at bed rest, unless he is febrile. Mental rest is also often prescribed for the patient in the form of various tranquilizers.

Administration of Drugs

Anticholinergic Agents — These are given in order to relieve cramps and delay emptying of the small bowel. Fairly high doses of the various drugs may be necessary. If, on the other hand, diarrhea becomes a major problem, a combination of diphenoxylate hydrochloride and atropine sulfate (Lomotil) is probably the preparation of choice.

Antibiotic Agents — Antibiotics were often tried, on the supposition that this disease looked and behaved much like a low-grade infection. Thus, in the early days of the availability of antibiotic agents, streptomycin and isoniazid were given to patients.[10] Now most clinicians would not use those drugs or the broadspectrum antibiotics unless a complication of the disease, such as the "blind-loop syndrome," were encountered.

However, when beneficial results were seen in ulcerative colitis from the use of salicylazosulfapyridine (Azulfidine), it became only a matter of time until it would be used in regional enteritis. Again, no controlled studies with this drug have been reported, but most clinicians now would be willing to at least try it. In general, however, results have not been nearly as encouraging as they were in ulcerative colitis. Patients receiving striking benefit have been few and far between, and the incidence of side effects is high. About 17% of patients[17] will have minor complaints of nausea, vomiting, indigestion, and headache. In many cases these will subside spontaneously. However, there has been an appreciable incidence of more serious side effects, such as fever, arthralgia, dermatitis, granulocytopenia, hemolytic anemia, and so on. The dosage used varies somewhat and has to be individualized for the patient, but an average schedule might provide for a dose of 3 to 4 gm. daily for two weeks out of four. During acute episodes, as much as 1 gm. every three hours may be given.

Corticosteroids — Adrenal steroids are again not as effective here as they are in ulcerative colitis. Some surgeons[12] have thought that steroids increase the difficulty of operation, making the tissues more friable and increasing the incidence of postoperative complications. There also has been some evidence of progression of bowel pathology in association with the use of steroids, even during times of subjective improvement. Since regional enteritis is a chronic disease and likely to require long-term therapy, one hesitates to embark on the use of drugs with such serious long-term effects. Despite all of these facts, a trial of steroid therapy may be indicated if the patient does not respond to conservative medical therapy, especially if he is not a surgical candidate. Some authors consider corticotropin (ACTH) superior to the hydrocortisone derivatives, especially in the acute phases of the disease; they would give their patients 80 units of ACTH intramuscularly daily and slowly reduce the dose during a period of months. The patient can give himself the daily injections much as a diabetic administers his own insulin. Other authors think that there is no particular advantage in ACTH; they use oral steroids. Tapering of the dose should be done quite slowly, regardless of the preparation selected. Full remission may take months. It should be emphasized that hemorrhage and perforation seem to occur more frequently in patients taking steroids.

Nitrogen Mustard — Winkelman and Brown,[18] at the Cleveland Clinic, have used nitrogen mustard in 13 cases of complicated and uncomplicated regional enteritis. Their results have been encouraging so far: of 13 patients, nine had satisfactory responses. However, it should be stressed that this was only a preliminary report, and routine use of nitrogen mustard in the treatment of regional enteritis should await further trials.

Irradiation

Palliative radiation to the abdomen has been used for this illness since the late forties for early cases, free of complications. The rationale behind its use is that it has an anti-inflammatory effect. Be that as it may, it has not been strikingly effective. In one series of 69 patients having such mild enteritis, 24 did well, eight did reasonably well, and 37 either did not respond or got worse.[10] Further, the incidence of diarrhea and obstruction is said to be high after this procedure. Most institutions are not using radiation therapy at this time.

Surgery

Only 26 years ago Cutler[19] remarked that the best thing a surgeon could do for a patient with regional enteritis would be to return him, intact, to the care of his internist. Yet in most large institutions, about 85% of patients having regional enteritis now undergo operation at least once. This change in attitude reflects a sober optimism which seems justified in the light of current statistics. In 1963 Barber and associates[20] reported from the Mayo Clinic a 10-year follow-up of patients operated on for regional enteritis. Of the 88, 22 required additional operations. But what is significant is that, at the end of the 10-year period, the state of health of those who had required re-operation was the same as that of those who had not needed re-operation. Ninety per cent of *all* of the patients were either in good or fair health; however, three had died of the disease and one had died immediately postoperatively. Statistics such as these may allow us a sober optimism when we refer patients with regional enteritis for operation.

Table 3 shows the indications for operation in two series of cases, 561 in all. In essence, the indications for operation are simply those complications of regional enteritis which cannot be treated medically. Duodenal ulcer was coincidental in those cases in which it was associated with the regional enteritis. The incidence of duodenal ulceration is no higher for patients having regional enteritis than for the population as a whole.

The operative procedure of choice in most experienced hands[12,21] seems to be

Continued

TABLE 3
Indications for Operation

Indication	Cases, % of Total	
	Series A (4)	Series B (8)
Obstruction	47	84
Abdominal mass	36	17
Internal fistulae	16	18
External fistulae	14	17
Intractability	9	0
Perforation	3	3
Bleeding	1	9
Duodenal ulcer	1	0
Abdominal pain	1	3

primary resection of the affected region, preserving as much colon as possible. In previous years by-pass procedures were in vogue; but since the operative mortality for both procedures is now the same, there seems to be no valid reason to perform a by-pass operation in most cases. Most surgeons now prefer to excise and remove diseased bowel rather than allow the intestinal fluid to be routed around it.

The improved mortality rate (less than 2%)[12,21] probably has resulted in large part from improved techniques in the preoperative preparation of the patient. Before operation, anemia, electrolyte imbalance, and dehydration should be corrected. If the patient is febrile, broad-spectrum antibiotics may be given.

Recurrences usually occur within two years of operation, but it may be as long as 20 years before some recurrences are seen. Just what constitutes a recurrence is a moot question that colors statistics. It should be taken for granted that someone who has had an extensive resection of small intestine may have a little diarrhea without the disorder being called a recurrence; further, the radiologic picture of a patient having had such a procedure may be a little more difficult to interpret than that of a normal person. If one then applies the criteria that mild diarrhea alone does not constitute a recurrence and that a mildly positive roentgenogram does not determine the existence of a recurrence in the absence of clinical confirmation, then the recurrence rate may be quoted as 35%.[3,12,20,21] About half of recurrences will be controlled by operation and half by medical measures. Finally, of the 18% who come to a second operation, about half will need a third procedure.

Whenever recurrent disease is present, the treatment of choice is medical, and operation should be offered only in the face of intractable complications.

Conclusion

In conclusion, then, what can we expect to happen to our patient with regional enteritis? If he has acute regional ileitis, he has a 50% to 90% chance of recovering completely and of having no recurrences. If he has any of the other forms of enteritis, he has about a 10% chance of doing well on medical treatment alone. On the other hand, he has about a 10% chance of dying either of his disease or because of operation for it. He has about an 80% chance of being operated on at least once, an 8% chance of needing only two operations, and a further 8% chance of needing three or more operations. And even if he is operated on, he has a 20% chance of having a recurrence, controlled at least reasonably well without operation.

Thus, in this disease, while the mortality is becoming acceptable, the morbidity remains frightening.

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May be secured from the author or the reprints.

When all else fails, try complaining. — Changing Times

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Clinical Path Conference

Liver and Kidney Failure in a 45-Year-Old Housewife

A 45-year-old housewife was admitted to St. Barnabas Hospital on May 7, 1966, with a one-week history of anorexia, nausea, and vomiting. For at least two weeks, she had become increasingly jaundiced and had noted enlargement of her abdomen. She had been in good health until four months previously when an attack of "flu" forced her to bed for two weeks. Before her "flu" attack, she had had periodic episodes of mild, colicky abdominal pain usually associated with ingestion of pork chops or fatty foods.

The patient denied contact with jaundiced persons, had not received recent transfusions or injections, and was not taking drugs. She used carbon tetrachloride occasionally in her housework but could recall no recent exposure. Until a month before her final illness, she had consumed a moderate quantity of alcohol and then stopped drinking "on her own."

The patient was a deeply jaundiced, asthenic white female. Her blood pressure was 130/80, her pulse 120 and regular, and her temperature 100°. The skin showed no angiomata. Except for tachycardia, the heart examination was normal. The lungs were clear to auscultation and percussion. A tender liver was palpated 10 cm. below the right costal margin; the edge was smooth and firm. The tip of the spleen was palpable. The abdomen was distended, but no fluid wave was elicited, and the bowel sounds were normal. No peripheral edema was observed. The lungs were clear to auscultation. The hands exhibited a fine tremor.

The laboratory data on admission showed a hemoglobin of 10.5 gm.%, a white blood cell count of 23,000 with 72 mature neutrophils and 23 band forms, and a sedimentation rate of 85 mm/hour. Studies related to the liver included a total bilirubin of 20.5 mg./100 ml. with a one-minute value of 15.1 mg./100 ml., a 4+ cephalin flocculation, a thymol turbidity of 3.5 units, a total protein of 5.9 gm.% with an albumin of 2.0 gm.% an alkaline phosphatase of 24 K-A units, a SGOT of 81 units, a LDH of 130 units (normal less than 100 units), a cholesterol of 173 mg./100 ml., and a prothrombin time of 22 seconds (control 14 seconds). Other serum values were a BUN. of 11 mg./100 ml., sodium of 126 mEq/l, chloride 91 mEq/l, potassium 3.0 mEq/l, and amylase 62 units. The urinalysis showed a specific gravity of 1.018, a 2+ albumin, a 4+ bilirubin, a negative urobilinogen, a positive urobilin, and 2-4 WBC/hpf.

X-ray studies — chest films, upper gastrointestinal studies, and barium enema — showed only an enlarged liver.

The patient did not improve and continued to have nausea and vomiting. An indwelling nasogastric tube returned clear gastric contents. A low grade fever of 99 to 101 degrees continued, and her pulse fluctuated between 90 and 120.

On May 12, the fifth hospital day, she underwent a laparotomy. Following the operation (a cholecystectomy and liver biopsy), her jaundice increased in intensity, and the serum bilirubin climbed to 30 mg./100 ml. Her fever persisted despite streptomycin and penicillin therapy, and the white blood cell count fluctuated between 20,000 and 30,000. Her abdomen became more distended. In addition, her BUN. began to increase. By May 23, the BUN. was 77 mg./100 ml. and on May 24, it reached a peak of 117 mg./100 ml. On May 26, she vomited coffee ground material, passed black stools, became hypotensive, and died.

Continued

Differential Diagnosis

Dr. Frank Martin*

Before I discuss the differential diagnosis, I have two questions. What was her mental state before death, and was the prothrombin time of 22 seconds repeated after giving Vitamin K?

Dr. Reece

Her mind was clear until the day of death. The prothrombin time was not repeated, and Vitamin K was never given.

Dr. Martin

We have a middle-aged woman who was in good health until four months before coming into the hospital. She says she consumed a moderate quantity of alcohol. I will assume this was an understatement.

She used carbon tetrachloride — a piece of historical information I will consider and then dismiss from the differential at the onset. The jaundice caused by carbon tetrachloride occurs within days or even hours after exposure. Decreased renal function and mental symptoms are noted immediately. The patients recover or die within a short time and do not have a two-month course as did this patient.

Physical Examination

Physical examination yielded two important observations — an enlarged liver and a palpable spleen. Both are often seen in hepatocellular diseases. An enlarged liver is uncommon in jaundice due to obstruction, but it is present in 30-50% of patients with cirrhosis and in a lesser percent of patients with hepatitis. A palpable spleen in a patient with jaundice is an important observation. I presume one can see a large liver and a large spleen in a patient with hemolytic anemia and jaundice but, for the most part, this is a sign of hepatocellular disease. The liver was definitely enlarged. It was down 10 cm., and it was abnormal because it was firm. The normal liver will have a smooth surface and may have a sharp edge, but it is not firm. A large firm liver in the presence of a palpable spleen makes me suspicious of hepatocellular disease.

I will go directly to the liver function tests. The bilirubin is that of obstructive jaundice. The one-minute value was 15 mgm.% with a total bilirubin of 20 mgm.%. The 4+ cephalin floculation is significant. It is a sensitive test which is positive in 80-90% of patients with marked hepatocellular disease. The thymol turbidity was normal. This doesn't rule out hepatocellular disease and, in perhaps 50% of patients with cirrhosis, it will be normal.

The next finding is of paramount importance — a total protein of 5.9 gm.% with albumin of 2 gm.%. It is significant because there are few causes of a marked decrease in albumin. In this country these are, in order of frequency, cirrhosis, glomerulonephritis, and perhaps multiple myeloma. Starvation can do the same thing, but for practical purposes a low albumin in a patient with jaundice is strong evidence of severe hepatocellular disease.

The SGOT was 81 units. This is not helpful to me. If it had been 1000 units, it would have been almost diagnostic for hepatitis, but an elevation of 81 units can be seen in either obstruction or cirrhosis. The LDH is given as 130 units. I really don't think that this test has much advantage over the SGOT, even though it is said to be more specific for liver damage. The prothrombin time of 22 seconds with a control of 14 seconds indicates severe hepatocellular disease, especially since it did not return to normal after the giving of Vitamin K.

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*Attending Internist, St. Barnabas Hospital.

History

At this point I would like to return to the history. Episodes of mild colicky abdominal pain associated with ingestion of pork chops and fatty foods are characteristic of gallbladder disease with stones. If a gallbladder is distended with a balloon at surgery, the patient has a sensation of fullness or a deep sense of discomfort but not colicky pain. He does not become nauseated or have vomiting. On the other hand, if the biliary tree is distended, nausea, vomiting and colic develop. In colic, stones are usually causing partial or complete duct obstruction. It is true that a cholecystitis can occur without stones. Perhaps this is due to a mucous plug with increased pressure in either the biliary or cystic duct. Colicky pain in cholecystitis without stones is rare.

Portal Cirrhosis vs. Postnecrotic Cirrhosis

Let us consider the patient before surgery with the information we have. First, a reasonable certainty of severe hepatocellular disease exists. Secondly, common duct obstruction and stones are probably causing the obstruction. As for the type of hepatocellular disease, portal cirrhosis is the most likely by all odds. Much has appeared in the literature lately about post-necrotic cirrhosis. Personally I don't know whether or not this is a definite entity apart from Laennec's cirrhosis. Clinically I don't think they can be differentiated. Perhaps there is a greater statistical incidence of alcoholism in portal cirrhosis and more hepatitis before post-necrotic cirrhosis, but statistics don't always help in managing patients.

The physical findings in both diseases are basically the same. One thing I don't understand about post-necrotic cirrhosis is that in most series, the number of palpable livers is given at about the same rate as cirrhosis, namely about 75%, but at autopsy the majority of post-necrotic livers are smaller. Why this discrepancy I do not know. From a clinical standpoint I can't differentiate these two types, if indeed they are different. Pathologically, I'll leave it up to the pathologist to describe the difference between the two. This is not an acute hepatitis. The liver function is too abnormal, especially the albumin of 2 mg.%. The globulin fraction is also helpful in separating cirrhosis from a prolonged hepatitis. The gamma globulin is more consistantly elevated in cirrhosis.

Indications for Surgery

In my opinion surgery was mandatory in this patient. I say that because I am convinced stones were present. If one leaves a common duct obstruction unrelieved, the liver function will degenerate, and it will degenerate much faster in an already impaired liver. The operation, however, should be done under local anesthesia. Using general anesthesia in the presence of marked liver dysfunction is a great risk. Also, certain types of analgesics are more dangerous than others, and those detoxified by the liver are the riskiest. Morphine is probably the worst offender. It is detoxified al-

Continued

most completely by the liver. In patients with severe cirrhosis, a small amount of morphine can act over a very prolonged period. Demerol, on the other hand, is excreted primarily by the kidneys and is safer. Long-acting barbiturates are excreted primarily by the kidneys and are safer than the short-acting ones which are detoxified by the liver. Paraldehyde is another offender; it is broken down almost exclusively by the liver and is dangerous in the presence of liver dysfunction.

This patient should have had surgery, but it should have been done under local anesthesia. The risk of leaving a common duct obstruction unrelieved is greater than the risk of operating in the face of hepatocellular dysfunction.

Hepatorenal Failure

The rise in the bilirubin after surgery is an ominous sign. Her fever persisted despite streptomycin and penicillin, and the white blood count was elevated. The white count of 20,000 was not necessarily due to infection — such as cholangitis. It was consistent with severe hepatic failure. A rising BUN. in the presence of hepatocellular disease portends disaster.

Baldus *et al.* wrote an excellent review of liver dysfunction with renal dysfunction in the March 1964 *Annals of Internal Medicine.*[1] They studied 25 patients with hepatic insufficiency who developed uremia. Nineteen of those 25 died. Why the combination is fatal is not known. They believe there is an impairment of the renal hemodynamics. Azotemia occurs before oliguria and before diminution in concentrating ability. In other words, the volume and specific gravity of the urine remain normal in the early phases of the azotemia. When oliguria does occur, the inability to concentrate may become impaired. One of two things must be happening: either there is more urea being formed or there must be an increased re-absorption of the urea from the kidneys. The latter seems most likely.

I think of liver diseases in terms of metabolic abnormalities. The liver is certainly the most metabolically important organ in the body. It is essential in the intermediary metabolism of all three basic substances, namely, carbohydrates, proteins, and fats. It is responsible for the synthesis of proteins, and it forms greater numbers of enzymes. The liver affects the intracellular metabolism of every cell in the body. As the liver dysfunction grows, nearly every cell in the body is impaired. Some organs are more sensitive to these changes than others — such as the brain and the kidneys. It seems to me what really happens is that the metabolic function of the kidney is impaired by liver dysfunction, that urea is reabsorbed, and that azotemia develops.

This patient did not go into liver coma. This does not mean she did not have severe liver failure. To be sure, coma is common in hepatic insufficiency. Clinically, there are several phases patients go through. They become euphoric, untidy, and slow down mentally. As time goes on, they become confused and stuporous but can be aroused. Finally, they cannot be aroused, and that, by definition, is hepatic coma.

There are many explanations for hepatic coma. Certainly ammonia can cause hepatic coma, but there are different types of hepatic coma, and ammonia-induced coma is just one type. In some patients with portal caval shunts, ammonia intoxication with flapping tremors is common. Patients who go into this type of coma often recover with therapy. I know one patient who went into 15 coma episodes and recovered from each. In his final episode the blood ammonia was not particularly elevated and he died.

On the other hand, I have never seen a recovery in patients in coma from acute yellow atrophy. They seem to have a metabolic abnormality in the brain. Coma is a grave sign. The vast majority do not recover.

Cholangitis

An ascending cholangitis with cirrhosis is a possible explanation for this patient's problems. She had fever, but usually in cholangitis both chills and fever exist. Chills, fever, increasing jaundice with pain are characteristic. It is entirely possible that this patient also had a cholangitis or one of its complications such as a liver abscess. Whether or not cholangitis was present, I am certain severe hepatocellular disease, probably cirrhosis, was present and that the uremia was related to the hepatocellular disease. She finally vomited coffee ground material. In the majority of patients we think that hemorrhage is due to ruptured varices, but other bleeding sites may be the culprit. In two of the patients in the series of Baldus et al., terminal hemorrhage was not related to varices.

In conclusion, I believe that this patient had severe hepatocellular disease; that it was most likely a form of cirrhosis; that there were stones present; that the patient died of liver dysfunction; that she may have had cholangitis. Cholangitis certainly cannot be ruled out, but I don't feel that it in itself was the main cause of death.

Dr. Frank Martin's Diagnoses

1. Severe hepatocellular disease, probably secondary to portal cirrhosis.
2. Cholelithiasis with possible cholangitis.
3. Hepatorenal syndrome (clinical).

Comments

Dr. Reece

You didn't mention the alkaline phosphatase of 24 K-A units or the cholesterol of 173.

Dr. Martin

The alkaline phosphatase of 24 K-A units suggests an obstructive type of jaundice. The cholesterol can be elevated in obstructive jaundice, but it was perfectly normal in this patient. With extensive liver damage, the synthesis of cholesterol is retarded, and it will not be elevated. It is uncommon to see the alkaline phosphatase elevated this high in cirrhosis. A superimposed cholangitis would account for the elevation. Dr. Hay, I said that colicky pain was good evidence of increased biliary or cystic duct pressure. Do you agree with that?

Dr. Lyle Hay*

I agree. She probably did have stones. But this patient bothered me because she was said to have had the flu. Patients with influenza can have intestinal symptoms with colic and with reference of pain to the right upper quadrant.

It is very important in these patients to get liver function tests early rather than to wait for several weeks. If you have a patient with severe liver damage from biliary tract obstruction, biliary cirrhosis or biliary

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*Surgery Department, St. Barnabas Hospital.

Continued

damage takes time to develop. In this patient with a four-week history of jaundice, the degree of her liver damage is more severe that that caused by common bile duct obstruction. I have seen patients who have had obstruction for six weeks without this degree of liver damage.

Patients with carcinoma of the pancreas and a progressive jaundice for four to six weeks do not show laboratory evidence of severe hepatocellular disease. These liver function tests were too abnormal to have come just from biliary tract obstruction. If you have cholangitis with a history of chills, fever, and toxicity; this process will be accelerated.

Dr. Harsharan Kaur*

Don't you think percutaneous cholangiographic study would be valuable in demonstrating obstructive process without resorting to surgery?

Dr. Hay

Liver biopsy or percutaneous cholangiography could have been used, but I agree with Dr. Martin that a liver biopsy under local anesthesia offers the most information at the least risk. You can directly visualize extrahepatic biliary tract and then do a cholangiogram.

Pathological Discussion

Dr. Reece

As Dr. Martin predicted, the autopsy showed severe liver disease. At operation the gallbladder contained stones. Fibrosis of the wall with round cell reaction was present. The extrabiliary channels were patent, and no stones were palpated in the common duct. The most striking observation was an enlarged, smooth, fatty liver. A Schleicher needle biopsy was done and showed a diffuse fatty infiltration (Figure 1). Numerous liver cells were replaced by fat, and I put forth a diagnosis of fatty metamorphosis.

I chose to call it fatty metamorphosis instead of portal cirrhosis with fatty change — although both were present. Fatty metamorphosis occurs more in young women alcoholics and is more rapidly fatal.[2] It is fre-

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*Resident in Surgery, Swedish Hospital.

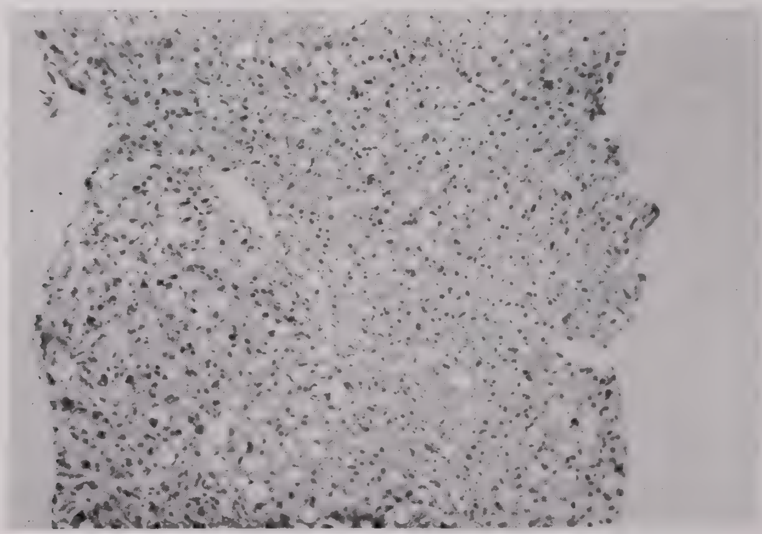

Fig. 1 — Schleicher needle biopsy of liver showing fatty change. H & E 35×

quently associated with right upper quadrant pain and with liver tenderness, and 25% of cases have leukocytosis. For mysterious and unknown reasons, many patients die with dyspnea and shock. Both fat emboli and hypoglycemia have been advanced as causes of death. Many of these patients present with a picture of obstructive jaundice and have an elevated alkaline phosphatase.

At autopsy we observed a deeply jaundiced, slender young woman. The lungs showed aspirated blood in the tracheobronchial tree, and the lower lobes were the seat of a necrotizing bronchopneumonia.

The liver weighed 2150 grams and was engorged with fat (Figure 2). The fatty changes were superimposed on a portal cirrhosis. Delicate bands of fibrous tissue linked the portal areas, and there was a minimal biliary duct proliferation. Inflammatory cells were few. There was no plugging of ducts with bile and no gathering of inflammatory cells around cholangioles. The spleen was enlarged and weighed 275 grams.

Whenever one deals with an alcoholic with cirrhosis, one must keep pancreatitis in mind. In this patient the pancreas was surrounded by fat necrosis, and the pancreatic parenchyma was pervaded by polymorphonuclear leukocytes and round cells (Figure 3). The incidence of pancreatitis in alcoholic patients varies from 20-60%.[3]

The kidneys weighed 250 grams. Each had a smooth bluish surface. Section of the kidney disclosed glomerular lesions which have been called "cirrhotic glomerulosclerosis" or "membranous and proliferative glomerulonephritis of cirrhosis."[4-5] It is characterized by hypercellular

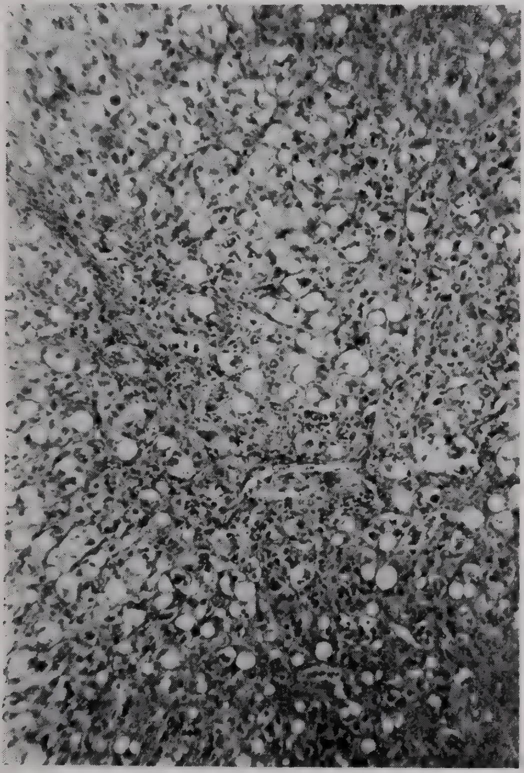

Fig. 2 — Low-power view of liver at autopsy. Fibrous tissue and fatty changes are evident. H & E 100×

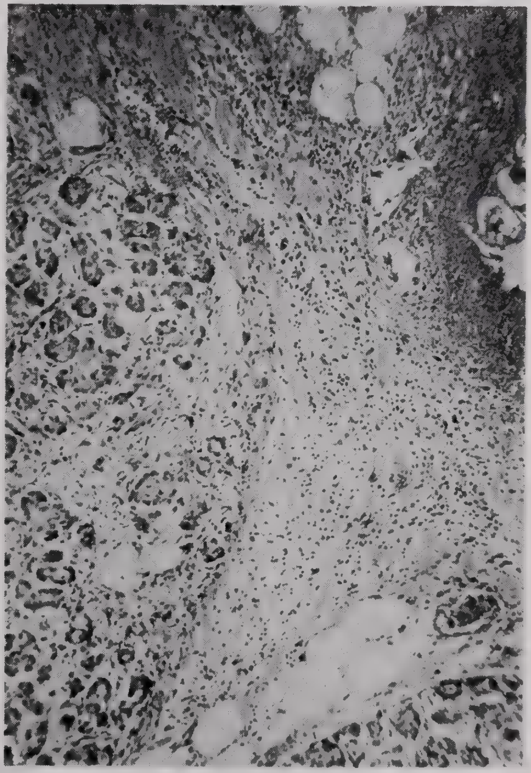

Fig. 3 — Edge of pancreas showing acute inflammatory cells and fat necrosis. H & E 35×

Continued

glomeruli and by thickening of the basement membranes (Figure 4). This change occurs in about 28% of terminal cirrhotics. It is not directly correlated with functional changes during life, and its meaning is uncertain.

A second lesion occurred in the tubules. The proximal tubules show diffuse degeneration which bordered on tubular necrosis (Figure 5). In the renal failure of cirrhosis, tubular changes may vary from mild tubular degeneration to necrosis. Similar tubular changes could be induced by hypokalemic, excessive osmotic load of sucrose and toxins, but I see no reason to evoke these causes. Although she had a low serum potassium, the tubule lacked characteristic vacuolar changes, and she did not put out dilute urine as patients do with hypokalemic nephropathy.

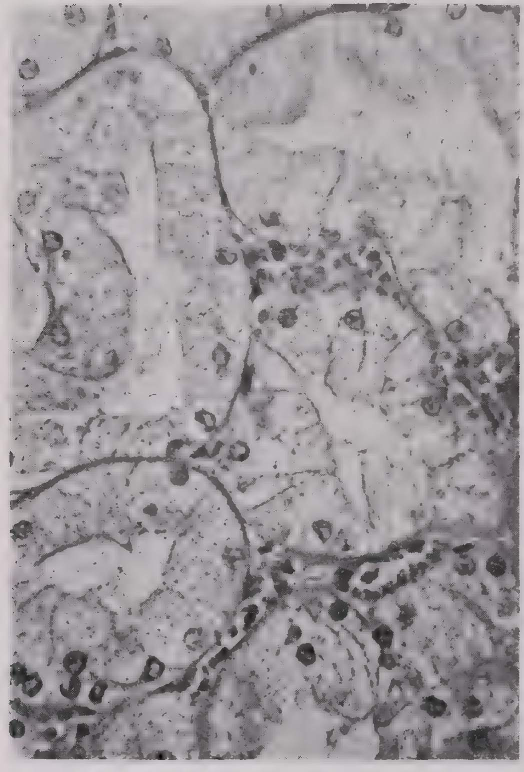

Fig. 4 — High-power view of proximal tubules showing degeneration of tubular epithelium. H & E 430×

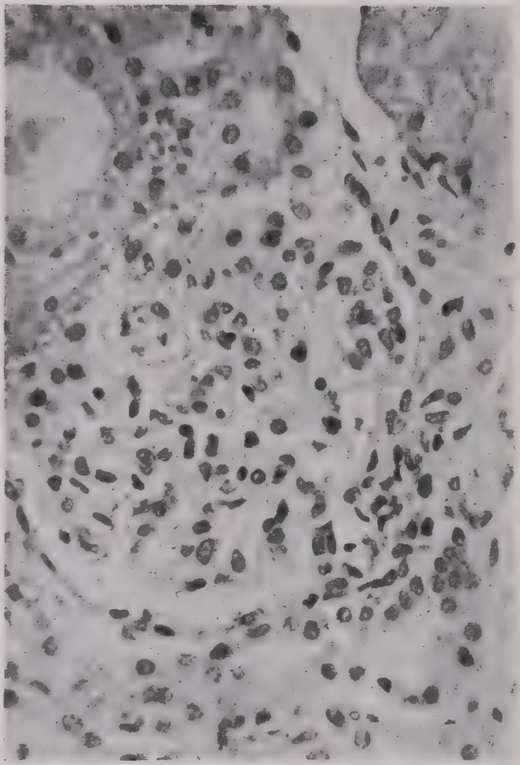

Fig. 5 — Hypercellar globerulus with capsular adhesion. H & E 430×

The hepatorenal syndrome is a legitimate term for describing combined liver and renal failure in terminal cirrhosis. It should not be used to describe liver and renal deterioration induced by toxins, by infection or by generalized sepsis and shock. The term "hepatorenal syndrome" was coined by surgeons. They noted that a certain group of patients developed oliguria and azotemia, with the preservation of otherwise good tubular function, after biliary tract surgery for obstructive jaundice.

This patient bled from an erosive esophagitis and gastritis. We did not find a ruptured varis, although she did have dilated submucosal veins (Figure 6).

Dr. Kaur

Do you think this patient would have done better if surgery had been

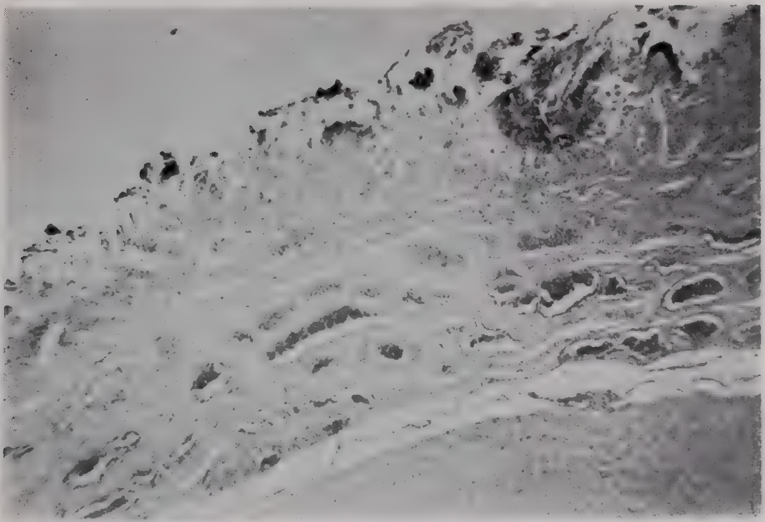

Fig. 6 — Erosive esophagitis with dilated submucosal veins. H & E 100×

delayed until the fatty cirrhosis was treated?

Dr. Hay

Yes, I had a young man who came in for a cholecystectomy with a similar history. He was a heavy drinker, and I palpated a big liver. He stopped drinking and ate well for three weeks, and then had his gallbladder out. At operation he still had fat in his liver. He had fever and jaundice after surgery, and his first three or four days were stormy. If we had operated on him three weeks before, he might not have survived the operation. I think he would have gotten over his fatty metamorphosis completely if we had just given him more time. If I had it to do over again, I would wait six to eight weeks before operating.

Final Anatomical Diagnosis

1. Portal cirrhosis with marked fatty change.
2. Acute pancreatitis with fat necrosis.
3. Bronchopneumonia.
4. "Glomerulonephritis of cirrhosis" and degeneration of proximal tubule epithelium.

Richard Reece, M.D.
Minneapolis, Minnesota

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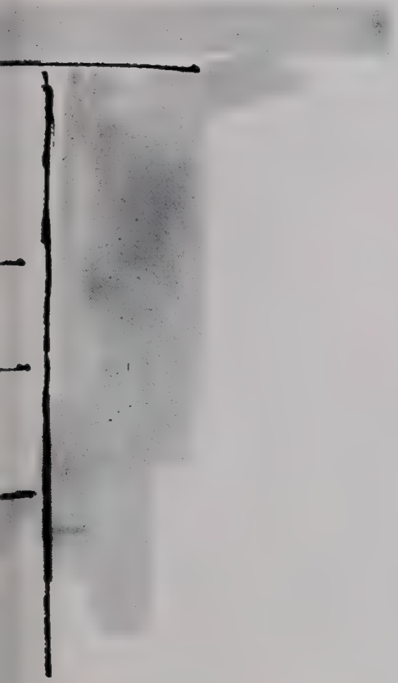
Nothing is clearer than what was discovered yesterday, and nothing more difficult to see than that which one will find tomorrow. — Jean Biot — 1774-1862

Neither repletion, nor fasting, nor anything else, is good when more than nautral.
— Hippocrates



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Grand Rounds

Bleeding Problems in Leukemia

OLE JERDE, M.D.
Medical Resident

HEMORRHAGE OF varying degrees is a frequent complication of leukemia and is generally a troublesome problem to the clinician treating the leukemic patient. While bleeding is generally associated with severe thrombocytopenia, it can occur at any platelet level. The purpose of this paper is to discuss various factors which may be involved in bleeding in the leukemic patient.

Causative Factors

Hemorrhage may be the initial manifestation of acute leukemia. Friedman et al.[1] reported on eleven confirmed and two probable cases of acute leukemia which presented with various bleeding problems ranging from easy bruisability to major hemorrhage. Boggs and his group,[2] in a series of 289 cases, found that cutaneous hemorrhages were present in 55 percent of the patients. Other series report bleeding problems present in 19 percent[3] and 47 percent[4] of patients at the time the diagnosis of leukemia was made.

Infection

Hemorrhage is a common cause of death in the leukemic patient and is second only to infection.[5] Hersh et al.[5], in a large series, reported massive hemorrhage to be present in 66.8 percent of their patients at autopsy. Since 1960 they have used platelet transfusions when indicated and have noted a decrease in fatal hemorrhage down to 38 percent. Hemorrhage was listed as the cause of death in 27 percent of Rivers' patients[3] and in 44 percent of Boggs' patients.[2] Acute promyelocytic leukemia seems to present a special problem, since the majority of deaths from that disease were attributed to hemorrhage.[6]

Disorders of bleeding may be classified as abnormalities involving the

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*Presented as a Medical Grand Rounds at Hennepin County General Hospital, May 2, 1966.

Continued

vascular bed, quantitative as well as qualitative defects in platelets, deficiencies in plasma factors, fibrinolytic abnormalities, or a combination of the above.[7]

The Platelet Level

Thrombocytopenia* secondary to decreased megakaryocytes in the bone marrow is the most common cause of bleeding in leukemia.[2,5,7,8] Since serious bleeding rarely occurs at platelet counts greater than 60,000 per mm^3, the above authors have termed this the critical platelet level. Most bleeding problems will occur at platelet levels below the critical level; however, the frequency and extent of hemorrhage at a given platelet count is quite variable. Some patients may have severe hemorrhage at counts near the critical level while other patients with severe thrombocytopenia may have no bleeding difficulties.[1,9,10]

Few studies have been made attempting to correlate platelet levels with degree and frequency of hemorrhage. Graydos[8] reported on 92 patients, comparing platelet levels and hemorrhage with seemingly good correlation. He found that when platelet counts were less than 1,000 per mm^3 overt hemorrhage was present 92 percent of the time. With platelet counts between 50,000 and 100,000 per mm^3 hemorrhage occurred 8 percent of the time. Severe hemorrhage rarely occurred at levels over 20,000 per mm^3, while petechiae, ecchymoses and epistaxis were quite common at this level. Grossly visible bleeding decreased in frequency along with a rise in platelet count. Graydos also noted that a decrease in platelet levels occurred from two to four days before the onset of bleeding. He felt that hemorrhage probably resulted from the thrombocytopenia; however, subclinical bleeding might have produced the thrombocytopenia which then caused the grossly visible hemorrhage. He went on to state that perhaps both the hemorrhage and the platelet level might be influenced by some other factor.

Platelet Morphology

In Friedman's series[1] platelet function studies were performed because all patients had normal platelet counts in the face of overt bleeding. Abnormal results were found in the prothrombin consumption test and in the thromboplastin generation test, and most of the bleeding times were also prolonged. The platelets were then studied morphologically with light microscopy and the electron microscope. There were marked variations in size, ranging from small, dense, round forms to large, globular, balloon forms with dendritic formation. On the basis of his studies Friedman postulated that abnormalities in platelet function might well be an early manifestation of acute leukemia.

Thrombocytopenia and Hemorrhagic Diathesis

Intracranial hemorrhage is a common cause of death in the leukemic patient and is generally due to severe thrombocytopenia associated with a hemorrhagic diathesis. However, it may be associated with blast cell crisis, which is a rapidly rising peripheral white blood count in which most of the cells are blast forms.[11] Of 13 patients who had blast crisis of more than 300,000 white blood cells, nine patients died within a few days following this crisis. Platelet counts in these nine patients ranged from 8,000 up to

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*See Test Your Word Score Page 1411.

205,000 per mm^3. At autopsy bleeding was found in the white matter of the brain. Tumor nodules were found which were surrounded by hemorrhage. It is felt that leukemic cells lodge in the blood vessels and infiltrate through the vessel walls into the surrounding tissues, causing necrosis of the vessel wall and predisposing to hemorrhage, even with normal numbers of platelets. The patients in this second group had less than 300,000 white blood cells per mm^3 and a smaller percentage of blast forms. Platelet counts in the second group ranged from 400 to 8,500 per mm^3. At autopsy bleeding was found to have occurred in either the subdural or the subarachnoid space and not in the brain substance as in the first group. In their series the blast crisis was an ominous sign, being associated with an immediate mortality rate of 60 percent.

Polysaccharide Level

Infection may be associated with a hemorrhagic tendency, the best known example being infection due to the meningococcus. Polysaccharides extracted from bacteria may inhibit the coagulation mechanism in a manner resembling heparin, which is a naturally occurring polysaccharide.[9] These authors studied polysaccharide levels in leukemic patients, most of whom had bleeding manifestations. Their studies indicated that bleeding rarely occurred if the platelet count was over 60,000 per mm^3 regardless of what the polysaccharide level was. Their studies also showed that most of the bleeding occurred in patients who had low levels of platelets and elevated levels of polysaccharides. There was no exact inverse relationship; however, these two factors appear to be independent and are additive or complementary in causing bleeding. While the anticoagulant effect of these polysaccharides may have been part of the problem, Freeman thought that vascular injury due to bacteria was more likely the mechanism. The vascular injury sequestered platelets in a patient who already had a borderline platelet level, decreasing the number of circulating platelets to where overt hemorrhage could occur. With appropriate antibiotic therapy bleeding ceased and the platelet counts gradually increased. In those patients in whom the infection could not be controlled, death was due to hemorrhage, overwhelming infection, or both.

Fibrinogen Metabolism

Another area concerns leukemia associated with abnormality in fibrinogen metabolism. As mentioned previously,[6] acute promyelocytic leukemia is characterized by severe hemorrhage, poor response to any therapy, and a rapid, short, progressive course. In Rosenthal's series[6] 10 of 17 patients expired during the first month, all but three dying of hemorrhage, either intracranial or gastrointestinal. Abnormal promyelocytes are the predominant cell in the bone marrow. These cells have immature nuclei along with different sized granules in their cytoplasm. These granules often have different staining properties. Platelet counts ranged from 10,000 to 60,000 per mm^3. Fibrinogen levels were low and varied from 40 to 170 mg. percent. Factor V levels were also decreased. Initially there was loose clot formation and poor trapping of red cells. Subsequently the clot contracted to a small firm size; there was no clot lysis. Because of the abnormal cells, in addition to the other deficiencies noted, Rosenthal preferred to call this "promyeloid" leukemia or "promyelocytic fibrinopathic" leukemia. One pa-

Continued

tient developed a hematologic remission with return of fibrinogen to normal levels.

Fibrinolytic Factor

Didisheim et al.[12] reported two patients with acute promyelocytic leukemia. Both cases had abnormal promyelocytes as the predominant bone marrow cell along with deficiencies of fibrinogen and factor V, and both patients developed hematologic remissions with improvement in the bone marrow along with return of fibrinogen and factor V to normal levels. Fibrinogen was given in an attempt to determine the etiology of the hypofibrinogenemia. Normally half of the amount given disappears from the circulation in four to six days; in this patient half was gone in 26 hours. Didisheim and his colleagues repeated the fibrinogen along with heparin; however, there was no change in the rate of disappearance. Occasionally coagulation time by the plastic tube method was less than normal. Fibrinolysins were not found. No thrombi were present at autopsy. They therefore concluded that acute promyelocytic leukemia is a distinct clinical entity.

Fibrinolysis has been reported in several different diseases including leukemia.[14,15] As described in Cooperburg's case,[14] the patient had symptoms of leukemia for about one month prior to admission, characterized by fatigability and occasional epistaxis. Petechiae and bleeding from the gums began four to five days prior to admission, with purpura and hematuria presenting on the day before admission. The fibrinogen on admission was 78 mg. percent. The patient expired during the first hospital day of massive intracranial hemorrhage. The clot formed normally but began to lyse in four hours and was complete in less than 24 hours.

Pisciotta[15] described a similar clinical picture with intracranial and gastrointestinal hemorrhage as the terminal event. Fibrinolysins were present for at least five days prior to death. Since fibrinolysin is also active against fibrinogen, prothrombin and factor V[14], a combination of these abnormalities, in addition to thrombocytopenia, readily explains the severe hemorrhage in the patients.

Defibrination Syndrome

The defibrination syndrome is well known and, while rare, has been observed in acute leukemia. Baker[13] reported a case of acute myeloblastic leukemia with widespread hemorrhage and a total clinical course of 20 days. Abnormally low levels of fibrinogen, plasminogen, and factor V were found. Heparin was given with cessation of bleeding along with improvement in the patient's sensorium. The fibrinogen, plasminogen, and factor V levels concurrently increased. Bleeding, however, occurred again two days later and the patient expired. Widespread intravascular clots were present at autopsy. The authors suggested that the leukemic cells may have had an effect on the increased coagulation.

Summary

1. Thrombocytopenia is the most common cause of hemorrhage in acute leukemia.
2. Deficiencies of various factors and functional platelet abnormalities, in addition to fibrinolysin, are probably more common in leukemia than is generally recognized.

Case Report

A 53-year-old white male was admitted on January 5, 1966, with complaints of mild anorexia, weakness, fever and epistaxis for approximately six weeks prior to admission.

Physical examination revealed a fundal hemorrhage on the right side, a harsh systolic murmur, and a palpable liver.

Admission hemogram showed 6.7 gm. percent hemoglobin; wbc. 800 with 16 percent neutrophils, 78 percent lymphocytes and 6 percent monocytes. Prothrombin time ranged from 13.2 to 18 seconds. Lee White clotting time was 17 minutes. An initial bone marrow biopsy was abnormal but nondiagnostic. A repeat bone marrow three days later was diagnostic of acute myelogenic leukemia. Megakaryocytes were decreased. The patient was treated with prednisone, 6-Mercaptopurine, Vincristine and Methotrexate; however, there was no response to therapy. He required two to three units of blood daily to maintain an adequate hemoglobin. Platelet counts were always less than 10,000 per mm.^{3} Stools were positive for blood on admission and became tarry after the first week. He developed subcutaneous hemorrhages which were confluent over his back. He expired on 1/25/66. An autopsy was not done.

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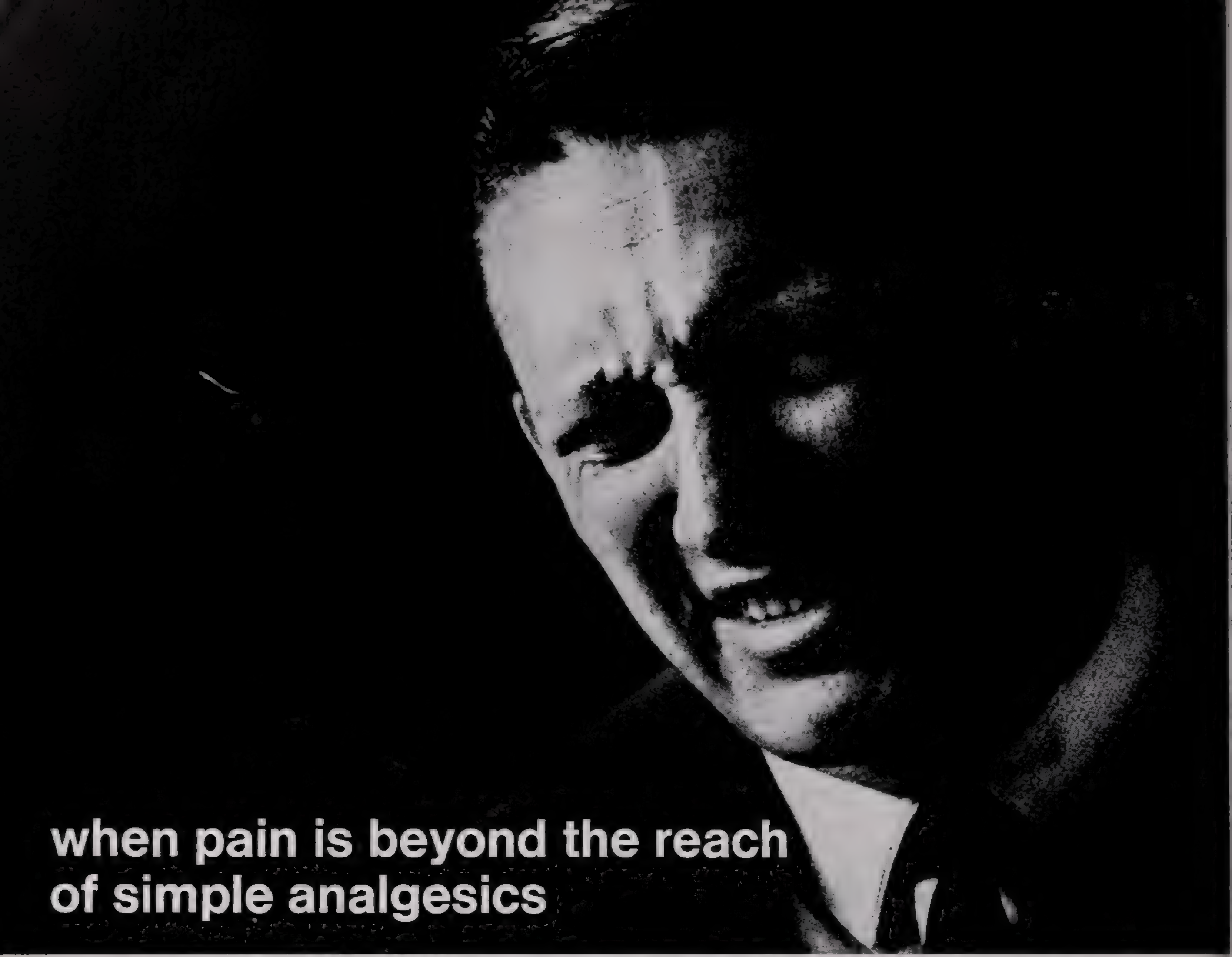
For Whom the Doctor Comes

It is not only for the sick man, it is for the sick man's friends that the Doctor comes. His presence is often as good for them as for the patient, and they long for him yet more eagerly. How we have all watched after him! What an emotion the thrill of his carriage-wheels in the street, and at length at the door, has made us feel! How we hang upon his words, and what a comfort we get from a smile or two, if he can vouchsafe that sunshine to lighten our darkness! . . . Over the patient in the fever, the wife expectant, the children unconscious, the Doctor stands as if he were Fate, the dispenser of life and death. . . . One can fancy how awful the responsibility must be to a conscientious man, how cruel the feeling that he has given the wrong remedy, or that it might have been possible to do better; how harassing the sympathy with survivors, if the case is unfortunate — how immense the delight of victory — William Makepeace Thackeray (1811-1863)

Triple-Faced

To the sick man, the physician when he enters seems to have three faces, those of a man, a devil, and a god. When the physician first comes and announces the safety of the patient, then the sick man says: "Behold a god or a guardian angel." — John Owen (1647)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Side effects have been minor. Occasionally gastric distress, weakness, sedation or dizziness occur. Reversible cholestatic jaundice has been reported on rare occasions. However, in 4,653 patients treated with chlormezanone, 97.7% had *no* side effects.[1] *Contraindication:* just one: sensitivity to aspirin. *Dosage:* Adults, usually 2 tablets three or four times daily. Children (from 5 to 12 years), 1 tablet three or four times daily.

1. Collective studies, Department of Medical Research, Winthrop Laboratories.

Winthrop WINTHROP LABORATORIES, NEW YORK, N. Y. 10016

Advances

Antibacterial Management of Infection Due to Gram-Negative Bacilli *

Part V. Some Infections of the Bloodstream, Cardiovascular System, Gastrointestinal Tract, Urinary Tract and Reproductive System

WILLIAM J. MARTIN, M.D.**
Rochester, Minnesota

Bacteremia

BACTEREMIA DUE to gram-negative bacilli is most commonly caused by members of the Enterobacteriaceae.[1-4] *Escherichia coli* organisms are responsible twice as often as are *Klebsiella-Aerobacter* organisms, and the remaining cases are most commonly due to *Proteus* organisms. Other possible pathogens of this group include *Paracolobactrum, Alcaligenes, Salmonella,* and *Shigella.* Bacteremia due to gram-negative bacilli not classified as Enterobacteriaceae and not causative of specific diseases may be caused by *Pseudomonas, Bacteroides, Haemophilus,* and *Achromobacter* organisms. As indicated previously, in serious infections due to these bacilli, empiric therapy with streptomycin and a tetracycline or kanamycin and chloramphenicol has been preferred. When microbiologic studies are complete, the empiric regimen is re-evaluated accordingly. For example, if *Pseudomonas* is identified as the pathogen, polymyxin B or colistin is substituted; if the patient has not done well and *E. coli* is reported as being susceptible to ampicillin and cephalothin on in-vitro testing, one of these drugs may be given to replace the empiric regimen.

In bacteremia due to either *B. fragilis* or necrobacilli, a tetracycline suffices. In bacteremia due to other organisms in the family of *Bacteroides* such as fusospirochetes or *Streptobacillus moniliformis,* penicillin is preferred.

Bacteremia due to *H. influenzae* is of higher incidence in children and has responded to streptomycin and a tetracycline, and also to chloramphenicol. Use of ampicillin or cephalothin warrants further investigation.

The drug of choice in typhoid fever currently appears to remain chloramphenicol.

In bacteremic brucellosis, streptomycin and a tetracycline given for two weeks are recommended; if only a tetracycline is given, there may be an appreciable incidence of relapse and perhaps an increased likelihood of brucellosis occurring at a later date unless the duration of therapy is considerably prolonged.

Of the bacteremias caused by *Pasteurella* organisms, tularemia responds to either streptomycin or a tetracycline. The same drugs are used conjointly in plague, but in bacteremia due to *P. multocida,* penicillin is preferred.

In bacteremia due to members of the tribe Mimeae, a tetracycline plus kanamycin, polymyxin B, or colistin is used at least until in-vitro susceptibilities are reported.

Patients with bacteremia due to *Vibrio fetus* are treated with streptomycin and a tetracycline.

Some Infections of the Cardiovascular System

Endocarditis and endarteritis[5] due to gram-negative bacilli have been relatively

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*The six parts of this paper were presented, in part, at the Symposium on Antibacterial Agents sponsored by the Southern California Society of Hospital Pharmacists, Los Angeles, California, May 2, 1965.

See Part IV. Minnesota Med 49:1309, 1966.

**Mayo Clinic and Mayo Foundation: Section of Medicine.

uncommon, but their incidence is believed to be increasing. After in-vitro susceptibilities are reported and if empiric therapy is unsatisfactory, ampicillin, cephalothin, polymyxin B, or colistin may have application. If the bacilli are sensitive to tetracycline or chloramphenicol, use of the agent is sometimes continued; but another agent to which the organisms are sensitive, such as colistin, should be given, since endocarditis and endarteritis require a regimen with a bactericidal effect. The regimen should be evaluated by means of serum bactericidal tests; and if the patient's serum containing the given antibiotics, when diluted 1 to 4, has an eradicative effect in vitro on the pathogen treatment, the regimen is continued for at least four weeks. *Pseudomonas* infection is most likely to occur after cardiovascular surgery, and a regimen including polymyxin B or colistin is recommended; but cure is not usual unless further operation can remove the nidus of infection. Endocarditis due to *H. influenzae or H. parainfluenzae* might require streptomycin-tetracycline therapy, or conjoint use of chloramphenicol and a bactericidal drug, such as ampicillin or cephalothin. Brucellar endocarditis is extremely rare, but streptomycin and a tetracycline are indicated. In endocarditis due to Mimeae, a tetracycline plus kanamycin, polymyxin B, or colistin is given, at least until in-vitro susceptibilities are known.

Suppurative pericarditis is more often due to coccal organisms but is rarely caused by gram-negative bacilli, including *P. tularensis*. Combined streptomycin-tetracycline therapy is used in tularemic pericarditis.

A cryptogenic* or primary mycotic aneurysm refers to the growth of organisms, usually *Salmonella* organisms or staphylococci, on an arteriosclerotic site resulting in suppurative arteritis which may progress to rupture. This variety occurs in older people in the absence of endocarditis; by contrast, the embolomycotic variety associated with bacterial endocarditis is usually due to streptococci. Surgery plus empiric antibacterial therapy are indicated; preoperatively, cephalothin may provide antibacterial coverage. After operation, therapy in keeping with in-vitro susceptibilities is given in an attempt to preserve the integrity of the arterial prosthesis.

Some Infections of the Gastrointestinal Tract

Fusospirochetal gingivitis may progress to stomatitis wherein the cavity is covered with ulcers underneath a pseudomembrane. Penicillin is preferred, but a tetracycline also is effective.

The Liver

Pyogenic liver abscesses usually are due to *E. coli* organisms, staphylococci, or streptococci, including enterococci; sometimes anaerobic organisms, such as *Bacteroides* and rarely *Brucella* organisms, are causative. Empiric regimens like streptomycin-tetracycline-nafcillin or kanamycin-chloramphenicol-penicillin provide "coverage" until microbiologic data are known. The latter regimen, because of its inclusion of penicillin G would likely have a more efficient anti-enterococcal effect. Since the tetracyclines are more concentrated in the bile than is chloramphenicol, they may be preferable in these and related infections. Hepatic photoscans may identify the abscesses before operation and also provide more objective follow-up.

Suppurative cholangitis usually reflects biliary obstruction due to stone, scar, or tumor. "Coverage" as suggested for pyogenic liver abscesses is given until microbiologic data are known.

The Gallbladder

In acute cholecystitis, similar "coverage" is given until the patient is afebrile at least 72 hours. Cholecystography is performed about one week after subsidence of symptoms and if the sedimentation rate of erythrocytes has begun to return to normal. When the gallbladder is not visualized, the study is repeated in six weeks. Repeated failure to visualize the organ or the finding of stones indicates the need for surgery.

The Peritoneal Cavity

Peritonitis after various intra-abdominal catastrophes or surgery also is often managed initially by such regimens as streptomycin-tetracycline-nafcillin or kanamycin-chloramphenicol-penicillin. It is obvious that peritonitis, like certain of the hepatobiliary infections mentioned previously, may be difficult to study microbiologically, and hence antibacterial therapy may necessarily be empiric. If the abdominal cavity is surgically explored, cultures of peritoneal fluid or tissue may allow substitution of a more definitive regimen. In most cases, peritonitis is due to a mixture of organisms including Enterobacteriaceae, *Bacteroides* and enterococci, and of course the possibility of *Clostridium* organisms should not be neglected. Blood cultures should always be obtained, as these may provide etiologic information as well as aid in gauging the extent of the bacterial invasion.

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*See Test Your Word Score Page 1411.

Gastroenteritis

Gastroenteritis from *Salmonella* organisms is managed by agents with systemic effect such as a tetracycline, chloramphenicol, and ampicillin, or by agents which are not well absorbed from the intestinal tract, such as paromomycin, neomycin, kanamycin, polymyxin B, and colistin, in keeping with cultural and in-vitro inhibition studies. However, since *Salmonella* infection may be associated with bacteremia and such complications as meningitis, pneumonia, and osteomyelitis, the agents with systemic effects may be preferable initially until more definitive microbiologic data are available. It should be recalled that *Salmonella* organisms are not uncommonly isolated from the urine of patients with gastroenteritis, especially women, and that use of antibacterial agents which are poorly absorbed on oral administration would not affect their urinary eradication.

There are data suggesting that antibacterial therapy of gastroenteritis from *Salmonella* organisms, by interfering with the function of the intestinal flora, prolongs the period during which stool cultures remain positive for *Salmonella* organisms.

Chronic hepatobiliary salmonellosis may be the essential problem in some persons having the carrier state. When the patient has gallstones, antibiotic therapy without cholecystectomy is often unsuccessful. Ampicillin and cephalothin are under investigation, but other regimens such as large doses of penicillin G, kanamycin, and colistin have been used with success. *Salmonella* organisms may also lodge in liver, bone, the urinary tract, aneurysms, the heart valves, and other sites. In cases of accessible areas of localized salmonellosis, surgical drainage is often diagnostically as well as therapeutically helpful.

Dysentery from *Shigella* organisms may respond to the sulfonamides, but in areas characterized by resistant strains, a tetracycline, ampicillin, or cephalothin may be preferable. *Shigella*, unlike *Salmonella*, rarely invades the blood, but about 50 cases of bacteremia from *Shigella* have been reported and this possibility at least warrants consideration. Furazolidone, neomycin, kanamycin, polymyxin B, or colistin sulfate given orally also may have use in nonbacteremic patients.

As aforementioned, it is disputed whether anti-bacterial agents such as the tetracyclines are useful in cholera. In this regard, World Health Organization reported a total of 81,400 cases of cholera throughout the world in 1964, representing an approximate increase in incidence of 20% over the total for 1963. The incidence of cholera is relatively high in Vietnam, particularly in Saigon.

Diverticulitis

Diverticulitis coli requires therapy active against Enterobacteriaceae and enterococci. In mild diverticulitis, a nonabsorbable sulfonamide like sulfaguanidine may suffice. Pericolic abscess may complicate severe diverticulitis, which may perforate and cause peritonitis. Regimens such as streptomycin-tetracycline-nafcillin or kanamycin-chloramphenicol-penicillin G provide "coverage"; but surgery, immediate or ultimate, has been required in 5 to 20% of patients. Surgery may also be required in certain complications (perforation, abscess, stricture) or when repeated attacks of acute diverticulitis occur.

Diarrhea due to enteropathogenic strains of *E. coli* and sometimes *Proteus*, *Klebsiella-Aerobacter*, and *Pseudomonas* organisms occurs most often in young children. These

Continued

pathogens along with various types of *Salmonella* and, less frequently, *Shigella* may be causative in nursery epidemics. Cocci are less often at fault. The tetracyclines and sulfonamides as well as drugs which are poorly absorbed from the intestinal tract, such as neomycin, kanamycin, polymyxin B, and colistin sulfate, have been used.

The bacterial causes of food poisoning include the Enterobacteriaceae, staphylococci, streptococci, and organisms of *Clostridia*. In the United States staphylococci are most commonly responsible, but in Europe *Salmonella* is a frequent cause. If the patient remains symptomatic, toxic, and febrile after six to eight hours, the initiation of empiric antibacterial treatment is considered. The use of neomycin, a nonabsorbable sulfonamide, or a tetracycline can be started and, after microbiologic data are known, therapy can be modified accordingly.

The Pancreas

In acute pancreatitis, wherein the patient is moderately or severely ill, antibacterial therapy is often given in an attempt to prevent suppuration, abscess formation, and other infectious complications such as pneumonia and bacteremia. Regimens like streptomycin-tetracycline-nafcillin or kanamycin-chloramphenicol-penicillin provide "coverage."

Clinical and biochemical improvement on long-term use of a tetracycline for two months or longer in some cases of Whipple's disease has been correlated with disappearance of bacilliform bodies from the mucosa of the small intestine as determined by serial biopsy specimens studied by both light and electron microscopy. Similar bacilliform structures undergoing phagocytosis have been described in the macrophages with which the intestinal mucosa and mesenteric lymph nodes are infiltrated. Attempts to culture a specific organism consistently have been disappointing. While there is basic agreement that use of antibacterial agents, such as a tetracycline, may be beneficial in the management of intestinal lipodystrophy, some investigators suggest that the bacterial agents are secondary invaders and that the primary factor involves an unknown, but perhaps cellular, defect in the intestinal mucosa. Workers who have assumed that these bacilliform bodies represent bacteria insist that the requirements for cultural growth have not been met.

Tropical Sprue

In cases of tropical sprue, hematologic and gastrointestinal remission may occur after a tetracycline is used. Perhaps intestinal floral changes with increased bacterial production of folic acid, or tetracycline-induced improvement of jejunal absorptive capacity with greater amounts of dietary folic acid being extracted, are responsible. It has been postulated that underlying intestinal stasis allows orad progression of the colonic flora and that antibiotic therapy corrects this secondary abnormality, while other investigators suggest that the inflammatory and atrophic changes in the enteric villi result from bacterial action and that a tetracycline permits the mucosa to recover and regain its ability to absorb dietary folic acid.

Since some patients having diabetic diarrhea and some having malabsorption associated with other causes, such as intestinal scleroderma may also be improved by use of a tetracycline, it is possible that in these situations, and in Whipple's disease and tropical sprue as well, control of bacterial proliferation in the small intestine is a nonspecific and common explanation for the efficacy of antibiotic therapy under these varying circumstances. Perhaps a primary defect so alters local resistance in these conditions that micro-organisms, including those of exogenous origin and those of the colonic flora, can overgrow in the small bowel, and improvement on antibiotic therapy then reflects elimination of these bacterial invaders. In this regard, it is appreciated that recent data would indicate that less than 1/3 of cultures of material aspirated from the small intestines of human subjects are sterile, and that organisms, usually streptococci and coliform bacilli, are isolated from the majority. If the above hypothesis is correct, it would concern increased numbers of organisms, and perhaps those not normally present.

The Spleen

Splenic abscesses may result from embolization in patients having bacterial endocarditis. Chronic abscesses, associated with evidence of calcification on roentgenograms, may be caused by tuberculosis, histoplasmosis, or brucellosis. In splenic brucellosis,[6] the regimen of streptomycin and a tetracycline may be ineffective without conjoint splenectomy.

Subphrenic or subhepatic abscesses may complicate such situations as appendiceal rupture, duodenal perforation, and postoperative biliary infections.[7] Subphrenic abscesses may be manifested by such thoracic findings as pleuritis, effusion, or pneumonitis; in other cases, such abdominal manifestations as pain, tenderness, and a mass may occur. *E. coli* is usually causative, but other Enterobacteriaceae and cocci may be present. Surgical drainage plus regimens such as streptomycin-tetracycline-nafcillin or kanamycin-chloramphenicol-penicillin are indicated. When microbiologic data are known after operation, antibacterial therapy is modified accordingly.

Perianal abscesses and anorectal fistulae usually require operation, and attempts at definitive therapy with antibacterial agents are unwise. Of course, when such lesions are associated with primary disease such as chronic ulcerative colitis or regional enteritis, then therapy of the underlying condition should precede consideration of surgery. Rarely, bacteremia due to gram negative bacilli occurs after operation. One should recall that a deep ischioanal or ischiorectal abscess is a cause of obscure fever.

Some Infections of the Urinary Tract

Infections of the urinary tract are of varied pathogenesis, symptomatology, and prognosis; consequently their antibacterial management is difficult to generalize. However, there are four commonly used regimens.[8]

Empiric Therapy

Preliminary empiric therapy, often in the form of sulfonamides, is given patients having acute infection without overt evidences of underlying uropathy or predisposing disease. In such cases a Gram-stained specimen of uncentrifuged urine may substantiate the presence of bacteruria. When therapy is given on this basis, the patient may be recovering when cultures are reported. In other patients, such as those allergic to sulfonamides, nitrofurantoin or nalidixic acid may be preferred. In certain infections, especially enterococcal ones, methenamine mandelate has application.

Prophylactic Therapy

Intermittent prophylactic therapy, usually with nonantibiotic antibacterial agents, is given five to 10 days or each month for six to 12 months to patients having acute recurrent infection after unrevealing investigation for underlying uropathy or predisposing disease.

Definitive Therapy

Definitive therapy is given for infections persisting after recent surgical correction of underlying uropathy wherein renal function is threatened, also for abscesses, conjoint bacteremia and the like. Antibiotics are generally used in these situations in accordance with microbiologic and urologic findings. Streptomycin and a tetracycline may be given until microbiologic data are known. When such data are known, ampicillin, cephalothin, kanamycin, polymyxin B, colistin, or chloramphenicol is considered against *E. coli.* Among the objections to use of chloramphenicol is the finding that the drug may be largely excreted in the urine in a conjugated and therefore perhaps inactive form. Excepting ampicillin, the same agents have use against *Klebsiella-Aerobacter* organisms. Kanamycin, chloramphenicol or cephalothin may be useful against *Proteus,* bacilli, whereas penicillin, ampicillin, and novobiocin are of use against *P. mirabilis.* Polymyxin B or colistin are the drugs of choice against *Pseudomonas.* A tetracycline is the drug of choice against *Bacteroides.*

Suppressive Therapy

Suppressive therapy is given patients who have chronic infection not susceptible to eradication in attempts to minimize renal damage and symptoms. Drugs may be given con-

Continued

tinuously, intermittently or alternately; alternate use of agents may minimize floral changes and bacterial resistance. The non-antibiotic antibacterial agents have use in some of these cases.

Patients with acute infections of the urinary tract are treated for at least one week after their clinical and cultural control; persistent infections warrant even longer treatment thereafter. Periodic re-examination ensures that the patient remains free of infection.

Some Infections of the Reproductive System

Fusospirochetal vulvovaginitis and balanitis occur in patients with lowered resistance in whom stomatitis due to these organisms eventuates in systemic invasion. Penicillin is preferred, but the tetracyclines are also effective.

Vaginitis due to *H. vaginalis* is somewhat obscure, but the "clue cells" are said to indicate its presence. Gram-stained smears and wet mounts may aid in detecting the bacilli, but their presence should be confirmed by cultures. A sulfonamide, a tetracycline, or ampicillin may be tried along with local therapy.

While puerperal fever classically represents streptococcal infection, occasionally staphylococci or gram-negative bacilli including *Bacteroides*, are causative. A regimen like penicillin-chloramphenicol-kanamycin may have empiric use in such cases. Cephalothin is being investigated.

Postabortal endometritis is usually due to gram-negative bacilli, but streptococci, staphylococci, or organisms of *Clostridia* may be responsible. Cervical smears may be helpful while awaiting cultural reports. A regimen such as penicillin-chloramphenicol-kanamycin is given, and 12 to 24 hours thereafter the uterus is emptied unless hemorrhage requires immediate operation. Cephalothin is being investigated.

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Respiratory Disease Contest

The Minnesota Thoracic Society in association with the Minnesota Tuberculosis and Health Association announces a prize contest for senior medical students, interns and resident physicians in Minnesota.

A. A prize of $200.00 is offered for the best paper submitted by a senior medical student or intern on some aspect of respiratory disease, preferably based upon laboratory or clinical investigation.

B. A prize of $300.00 is offered for the best paper submitted by a resident physician based upon clinical or laboratory investigation in the area of respiratory disease.

The sponsors reserve the right to make no award in either or both categories, based upon the opinion of the judges. Further information may be secured from the Secretary. Entries should be submitted by June 15, 1967, to: David E. Dines, M.D., Secretary, Mayo Clinic, Rochester, Minn.

Medical Ethics

Medicine — a Profession or a Business?

*Address by James Z. Appel, M.D.**
First National Congress on Medical Ethics
Chicago, Illinois
March 5, 1966

The AMA Judicial Council — in connection with this first National Congress on Medical Ethics — plans to publish and distribute a series of essays on significant topics involving medical ethics. The first article in that series, dealing with the question of what the profession should do about the incompetent physician, appeared in the December 20, 1965 issue of the Journal of the American Medical Association.

Medical Incompetence

Medical incompetence is the inability to practice good medicine by modern methods, either because of mental or physical condition, or failure to keep up professionally.

Although incompetent physicians constitute a small minority of the profession, their potential dangers are disproportionate to their numbers. Over the past five years a large proportion of disciplinary actions by state medical boards has been based on various forms of incompetency.

Eight out of 47 state medical societies responding to a survey have provisions in their constitutions or bylaws for disciplinary action against a member for incompetence. Moreover, the laws of only 18 states make specific provision for disciplinary legal action because of physical or professional incompetence. The accredited hospitals, however, do have the authority to deal with incompetent physicians, and the staffs of these hospitals are more and more accepting their responsibilities.

Recommendations

1. The local hospital staff is the logical body to control the incompetent physician.

2. If the incompetent physician proves recalcitrant, the hospital staff should next turn to the grievance committee of the local or county society.

3. Only if efforts at the local level fail should the state society be asked to deal with the case.

4. Where there is convincing evidence that the incompetent physician has violated the law, the hospital staff should refer the case directly to the board of medical examiners.

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*Past President American Medical Association.

Continued

5. The hospital licensing body, by regulation and, if necessary, by legislation, should make every effort to apply the criteria of the Joint Commission to the fringe hospitals which are unaccredited.

6. Every medical practice act should specify incompetence as grounds for disciplinary action.

7. Although most problems are best handled at the local level if possible, there should be the closest cooperation among the hospital staff, the county and state medical societies and the boards of medical examiners.

This matter can not be left entirely up to the hospital staffs. The county societies must be more vigilant and active in dealing with the problem of incompetence.

The Authority of the State Board

It is understandable that one's immediate confreres might be hesitant to initiate any drastic action against a fellow physician who in the past has had an enviable record but who because of age or other form of adversity falls behind the mainstream of competency. The jurisdictional mechanism available to the state or national organization will stimulate activity at the local level.

The authority and activity of the state boards must be increased. Up to this time the principal function of state examining boards has been in the area of licensing. Two days of examination is a very inadequate method of determining a man's qualifications for medical and surgical practice, not only at the time of examination but also for the rest of his life; however, it is the only method we have.

It is doubly necessary to strengthen our medical practice acts because some incompetent physicians are members neither of a hospital staff nor of a medical society. These are the most dangerous kind, and they can be controlled only by the state boards.

Medical Ethics

As we move ahead in our expanded program of medical ethics, the essential, vital ingredient is the spirit of professionalism.

Most of us know, but rather tend to take for granted, the fact that a profession is primarily a calling for public service. For the conscientious doctor this involves a great deal of self-denial. The well-being of the patient comes ahead of the personal interest of the physician.

Another characteristic of our profession is that it is willing to accept and to exercise its responsibility of self-discipline and self-elevation of standards of quality. This First National Congress on Medical Ethics is evidence of the organizational acceptance of such responsibility. Our goal is to obtain maximum, *individual* recognition and acceptance of that responsibility.

If medicine remains true to its professional ideals, the public will have confidence in us and will not seek to protect its "interests" through politicians, by legislation or in other ways. Conversely, to the extent that we drift away from the principle of public service, the public might develop feelings of unrest and dissatisfaction which could lead to the conversion of medicine into a new kind of "public utility." Today there are more professions and professional people than ever before, and the trend toward more professionalism will probably continue to accelerate as society becomes more complex.

Professionalism

We must bear in mind that the world is debating the question of how society should be organized. Should it be organized for the individual, with maximum freedom, opportunity and responsibility for every person, or should it be organized for the group or state — with the individual subordinate to a government which dominates and controls most social, economic and political decisions?

The spirit of professionalism, like the sense of individuality, will have a strong influence on the ultimate answer. For us in medicine, as we face the many problems and challenges that confront us, one of our major responsibilities is to stimulate and nurture a genuine sense of professionalism — professionalism as a way of life.

In this connection the Journal of the American Medical Association pointed out recently that the famed scientist, Vice Admiral H. G. Rickover, reminded us last year that ours is a truly liberal and humanistic profession.

"Of all technologies," Admiral Rickover said in his Granada Lecture before the British Association for the Advancement of Science, "that of the physician has benefited man most and harmed him least. The stringent standards set by the profession and by society for the education and professional conduct of physicians account for this happy circumstance.

"Not only is no one permitted to practice who has not given proof of his competence, but physicians must also be broadly, liberally, humanistically educated men and women. This gives them perspective in evaluating their professional actions, an ability to see these actions against a humanistic background."

As the Journal said, the real significance of the Admiral's remarks lies in the fact that they were not intended as tributes to the medical profession, but rather as ideals for engineers — in the hope that they too would find it possible "to act with the same sense of professional responsibility and service to humanity which is characteristic of good physicians."

This independence of professional judgment cannot be taken for granted. "It lies," as Admiral Rickover reminds us, "in the determination of the medical profession to resist lay interference and its success in winning this point."

Service to Humanity

We will resist further interference and win our point only by emphasizing and maximizing the professional aspects of medicine and by deemphasizing and minimizing the business and financial aspects.

As individuals and as a group, we must constantly bear in mind the basic principle that "the primary object of the medical profession is to render service to humanity; reward or financial gain is a subordinate consideration." This points up the sharpest, greatest difference between medicine and business.

Most people do not expect a businessman to be motivated primarily by any other desire than that of making money. If it so happens that the principles of service and altruism help him toward that goal, so much the better. However, if sharp practices and deception, within legal limits,

Continued

enable him to achieve his objective more profitably, the public usually accepts these facts — possibly with resentment but not with great surprise or deep feelings of betrayal.

As Dr. Leonard W. Larson, past president of the AMA, pointed out in his inaugural address in 1961, the professional spirit is an unchangeable force in medicine. While its outward forms and applications may change with the course of history and alterations in the human environment, its essence is unchangeable, indestructible.

When the essence of that spirit is diluted or destroyed, either in an individual physician or in a nation, medicine ceases to be a profession in the highest sense of the word. Without the true professional spirit, the practice of medicine becomes simply an occupation, a way of earning a living.

The really good doctor, guided by the professional spirit, will always remember that medicine exists for just one purpose — to serve humanity — and he will strive for excellence in meeting that purpose. No matter how or to what degree the scientific and socio-economic patterns of medical practice may change in the future, we have the responsibility of preserving and invigorating the essence of the professional spirit.

Syphilis and History

History has been profoundly influenced in some cases by the effects of syphilis upon rulers. Ivan the Terrible of Russia suffered from cerebral syphilis, which drove him to deeds of horrible cruelty. The reign of several of the Tudors in England was marked by the almost unmistakable effects of syphilis. Henry VIII had a series of still-born children, strongly suggestive of the syphilis with which he was said to be infected. His son, Edward VI, died at an early age of what appeared to be a combination of congenital syphilis and tuberculosis. His daughter Mary — Bloody Mary — shows in her pictures the facial expression quite typical of the congenital disease. Henry himself had an abscess in his thigh, probably syphilis of the bone, which troubled him for many years. His marked sensuality developing in middle life and his blood-thirsty habits of divorce are strongly suggestive of cerebral syphilis. What a difference in the Tudor reign modern methods of treating syphilis might have made! Even Henry the VIII, after enduring the heroic treatment for syphilis current a hundred years ago, might have been thus converted into a misogynist as Arthur Schopenhauer was said to have been.*

The astrologers, having observed that syphilis invaded those parts of the body which they believe to be under the influence of Venus, called the disease *lues venerea,* or venereal infection.**

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*Haggard, Howard W., M.D.: Devils, Drugs, and Doctors. Blue Ribbon Books Inc. New York City, 1929, p. 244.

**Ibid, p. 245.

Ammonius

A surgeon of Alexandria in the third century B.C. He invented an instrument for breaking up such stones in the bladder as could not be extracted after incision. He is surnamed "the lithotomist."—Dorland's Medical Dictionary

Abstracts, Briefs and Commentaries

GASTRIC HYPOTHERMIA FOR HEMORRHAGE

Though gastric hypothermia for the cure and treatment of ulcer has not been extensively accepted, a simple method of gastric hypothermia for the control of massive hemorrhage of the stomach has been demonstrated by Hubbard to be of definite value in fifteen patients who would otherwise have been subjected to emergency operation for the control of the bleeding.

A size 18 French plastic nasal tube was passed through each nostril to the stomach. One tube was connected to a suction of low power; the other was connected by a rubber tubing to an open-end flask suspended from an intravenous stand. A Murphy drip was inserted so that the rate of flow could be evaluated, and an electrolyte solution containing .745 grams of potassium chloride and 2.0 grams of ammonium chloride per liter was used as the irrigating solution. This was buffered to a ph of 7.4 with sodium bicarbonate, as originally suggested by Wangensteen. Chipped ice was added to the solution, and 3,000 to 4,000 cc. of irrigating fluid was run through the stomach over each four-hour period. The solution was removed from the stomach at the same rate, either by low suction or by gravity.

Control of the gastric bleeding was provided in all 15 cases within a period of 24 hours. In those cases in which the inflow temperature was measured, it was found to be from 1 to 4 degrees centigrade, and the outflow temperature was from 18 to 21 degrees.

Editor's Note: This relatively simple lifesaving measure can be carried out without special equipment and certainly should be worth a trial in any patient who enters the hospital with massive gastric hemorrhage.

Crampton et al., who carried out a somewhat similar study on 60 patients, in which they used a Swanko gastric hypothermia unit and a stomach-shaped balloon, circulating a mixture of equal parts of 90 percent alcohol and water through the coaxial tube, were able to obtain control in 83 percent of their patients. The highest instance of control was obtained within a period of 24 hours; those that required more than 24 hours to control the initial bleeding had rebleeding while in the hospital. Because of this Crampton and his associates advocated that emergency surgery should be performed whenever possible if the patient initially controlled by hypothermia rebleeds during hospitalization.

Continued

Editor's Note: In the 15 cases reported by Hubbard, the cold electrolyte solution came in direct contact with the mucosa of the stomach, whereas in the cases reported by Crampton et al. only the balloon was in direct contact with the stomach mucosa. It may be that mechanical washing associated with cooling, as observed in Hubbard's group, could be a factor in more effectively controlling the gastric hemorrhage. It would seem that Hubbard's method is worth additional trial.

Carl O. Rice, M.D.
Minneapolis, Minnesota

T. Brannon Hubbard, Jr., M.D.: A Method of Gastro Hypothermia. Surgery 59:670, 1966.
Ray S. Crampton, M.D., Joseph R. Cali, M.D., Donald J. Shutello, M.D., John P. Glaubitz, M.D.: Observation on the Duration and Result of Local Gastric Hypothermia in the Management of Active Hemorrhage. Surgery 59:673, 1966.

TREATMENT OF HYPERTENSION

A follow-up study of 97 hypertensive patients with group 3 hypertension (or retinopathy) and 64 patients with malignant (group 4) hypertension clearly demonstrated that medical treatment improves the prognosis, although the mortality rate remained disappointingly high. The 5-year survival rate was 37.5% for patients with group 3 retinopathy and 28.6% for patients with malignant hypertension. Inadequate control of blood pressure, cessation of therapy, short duration of hypertension, and significant azotemia were associated with worse-than-average mortality rates. Effective treatment not only prolonged life but led to the regression of retinal hemorrhages, exudates and papilledema, but control of the hypertension did not seem to influence favorably those complications that are due to atherosclerosis, especially cerebrovascular accident. More than 10% of the survivors suffered cerebral vascular accidents, and this complication was the leading cause of death in this series. The marked relationship found between the degree of control of hypertension and longer survival suggests that more effective and better tolerated drugs will further improve the prognosis in severe hypertension.

Courtesy of References and Reviews
Journal of the American Medical Association

Farmer, R., Gifford, R., and Hines, E.: Arch Intern Med 112:118, 1963.

GASTRIC LYMPHOMA

Two pathologists made a retrospective survey of 71 patients with gastric lymphoma. At the time of diagnosis 65 patients had primary gastric tumors and six were associated with diffuse disease. Most patients had less than six months of symptoms. The five-year and ten-year survival rates for primary lesions were 59 and 28 percent. The best prognosis occurred with small, superficial lesions confined to the stomach. In long-term survivals, lymphoma of the stomach is not necessarily a manifestation of systemic disease.

Richard Reece, M.D.
Minneapolis, Minnesota

Joseph, J. I., and Lattes, R.: Gastric Lymphoma. Amer J Clin Path 45:653, 1966

VASECTOMY

Vasectomy is a common method of contraception which previous investigations have found to be well accepted by most patients. However, because of occasional reports of adverse changes in sexual functioning, psychological adjustment, and family relationships, Drs. Ziegler and Rodgers have investigated the psychological sequelae of vasectomy. In a preliminary study they administered the Minnesota Multiphasic Personality Inventory (MMPI) to a large group of patients both before and after they underwent vasectomy, and postoperative changes in MMPI scores suggested that these patients had become depressed and anxious. In order to confirm this impression, the authors interviewed 42 couples before and after the husband had undergone vasectomy and another 42 couples before and after the wife had received a prescription for an ovulation-suppressing drug. In addition, four months after the initial interview, both groups were asked to complete the California Personality Inventory, the Scripps Clinic Self Description Scale, the MMPI, and the Scripps Clinic Child Rearing Attitude Scale. At the time of the second interview, both groups expressed satisfaction with the contraceptive technique prescribed, the vasectomized husbands even portraying themselves as being more decisive and more inclined to form close, permanent interpersonal ties than before surgery. Indeed, item changes on the self-description inventories suggested that the vasectomized husbands were more masculine than the husbands in the control group and that the wives of the vasectomized husbands had assumed a more complementary and compliant marital role than the wives in the control group. However, as in the preliminary study, changes in postoperative MMPI scores contradicted this impression. Though psychological disorganization of the vasectomized men did not occur, test results indicated unfavorable personal and psychological adjustment.

Thus, the data gathered by Drs. Ziegler and Rodgers suggest first that vasectomized patients uniformly report good results and picture their postoperative psychological health as improved, and second, that postoperative psychological tests do not confirm these assertions but, instead, show that vasectomy is often followed by troubled, anxious, and depressed mental states. It appears that men who undergo vasectomy tend to deny or rationalize fear and concern over this procedure and to claim a more favorable outcome than is really the case.

James Janecek, M.D.*
St. Paul, Minnesota

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*Director of In-Patient Psychiatric Services, St. Paul Ramsey Hospital, Assistant Professor, Department of Psychiatry, University of Minnesota.

Ziegler, F. J., and Rodgers, D. A.: Effect of Vasectomy on Psychological Functioning. Psychosom Med 28:50, 1966.

SONS OF ALCOHOLICS

To obtain indirect evidence regarding the personality of potential alcoholics, sons of alcoholic men were studied by a 36-item behavorial questionnaire constructed to measure personality traits common in alcoholics. Forty-one sons of alcoholics were compared with 123 matched controls by classroom teachers. Contrary to the hypothesis tested, sons of alcoholics were rated less personable and more overtly aggressive than the controls. The results

Continued

were interpreted as showing a passive-aggressive personality preceding and possibly leading to alcoholism.

Courtesy of References and Reviews
Journal of the American Medical Association

Aronson, H., and Gilbert, A.: Arch Gen Psychiat 8:235, 1963.

ANESTHESIA IN ASTHMATICS

In a continuous three-yr. investigation of 220 anesthetics administered to 196 asthmatics who were studied for operative and postoperative morbidity and mortality, the significant findings were these: (1) Complications were more frequent in the asthmatic than in the nonasthmatic surgical population. (2) Approximately 75% of the complications were pulmonary. (3) Such complications were more common in asthmatics who received (a) a high spinal anesthesia for intraperitoneal surgery or (b) the combination of thiopental induction with cyclopropane for maintenance but not necessarily when these agents were used separately. (4) Halothane anesthesia resulted in the fewest complications. (5) There was no correlation between the severity of asthma and the complication rate, but there was a higher incidence of complications with longer surgery and duration of anesthesia, especially for surgery of the abdomen or chest. (6) Male asthmatics encountered significantly more complications than females.

Courtesy of References and Reviews
Journal of the American Medical Association

Gold, M. and Helrich, M.: Anesth Analg 42:283, 1963.

RADIATION EFFECT ON THYROID

A group of adult patients, treated by roentgen rays for diseases of the thyroid, was followed for 10 to 35 years to determine the possible carcinogenic effect of such radiation on the thyroid gland. This group was compared with a series of patients similarly treated during adolescence and with another group treated in childhood. A direct relationship between roentgen therapy to the neck region and the subsequent development of thyroid cancer appears to exist in those treated in childhood and adolescence. The data now available suggest that the younger the patient when treated, the greater the possibility of development of thyroid carcinoma. The data also indicate that the interval between radiation and the development of carcinoma is considerably less in children than in adolescents. Roentgen therapy does not appear to be a carcinogenic factor in adults.

Courtesy of References and Reviews
Journal of the American Medical Association

DeLawter, D., and Winship, T.: Cancer 16:1028, 1963.

A Face Is Really Many Generations

Every human face is a living composite of countless faces — generations and generations of faces. And any living face, well watched by love or hate, will reveal a hundred different aspects.

The more familiar we become with any common face, the more astonishing the multitude of transformations we observe in it, the more bewildering its fugitive subtleties of expression.

Death itself may bring into the countenance some strange expression never noticed during life.—Lafcadio Hearn

The Doctor's Workshop

Two Technical Aids in Wound Closure

A WEAK, easily torn peritoneum is an exasperating problem in abdominal wound closure during surgery. While the anesthesiologist is decreasing the anesthesia so that the patient will not be obtunded in the approaching post-anesthesia period, the surgeon is struggling to pull together a layer which tears with every stitch (Figure 1). To obviate this problem the following simple measure has been employed.

If there appears to be tension on the peritoneum, an interrupted suture of heavy silk or braided wire is placed in the fascia in the mid-portion of the wound and the suture is tied. This places the tension on the strongest layer of the wound and allows secure, easy closure of the peritoneum.

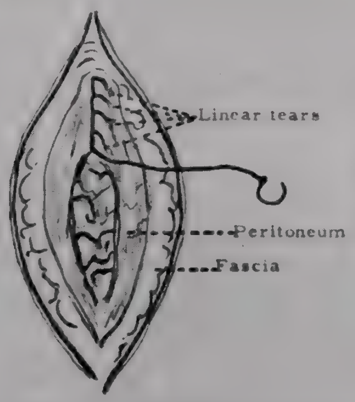

Fig. 1 — Usual Technique of Peritoneal Closure.

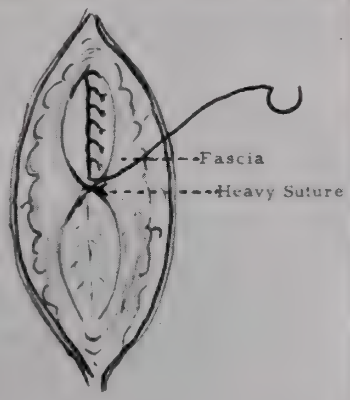

Fig. 2 — Peritoneal Closure with Center Fascial Suture.

Closure of the subcutaneous fat in an obese patient can be an arduous task. A commonly used method (Figure 3) involves multiple layers of interrupted plain catgut sutures placed with a round curved needle so that circular "bites" of tissue are taken. This technique of rotating a curved needle through tissue is essential in many areas and, naturally, becomes an automatic motion with surgeons. However, when this technique is applied to the subcutaneous fat, large areas are compressed, reducing blood supply and predisposing to necrosis and abscess formation. In addition, wounds

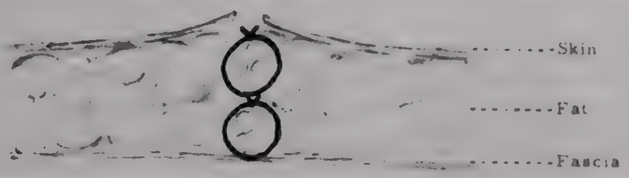

Fig. 3 — Usual Technique of Subcutaneous Closure.

Continued

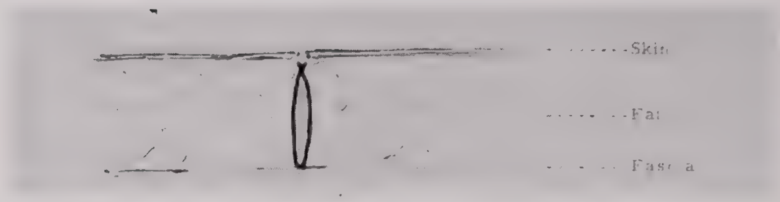

Fig. 4 — Subcutaneous Closure with Vertical Suture.

closed in this manner tend to gape and create a widely spread scar.

To correct these defects and obtain an anatomical closure, the suture, on a large curved needle, is passed from the skin along the edge of the fat to the base of the wound and brought up on the other side in a similar manner. One row of these sutures placed one to two centimeters apart closes a layer of fat of any thickness, with no gaping and a minimal amount of fat compression.

J. B. Brainard, M.D., M.S.
St. Paul, Minnesota

Dr. Carter's* Prescription for Rheumatism, Etc.

"Take a young fat dog and kill him, scald and clean him as you would a pig, then extract his guts through a hole previously made in his side, and substitute in the place thereof, two handfuls of nettles, two ounces of brimstone, one dozen hen eggs, four ounces of turpentine, a handful of tanzy, a pint of red fishing worms, and about three-fourths of a pound of tobacco, cut up fine; mix all these ingredients well together before deposited in the dog's belly, and then sew up the whole, then roast him well before a hot fire, save the oil, annoint the joints, and weak parts before the fire as hot as you can bear it, being careful not to get wet or expose yourself to damp or night air, or even heating yourself, or in fact you should not expose yourself in any way."**

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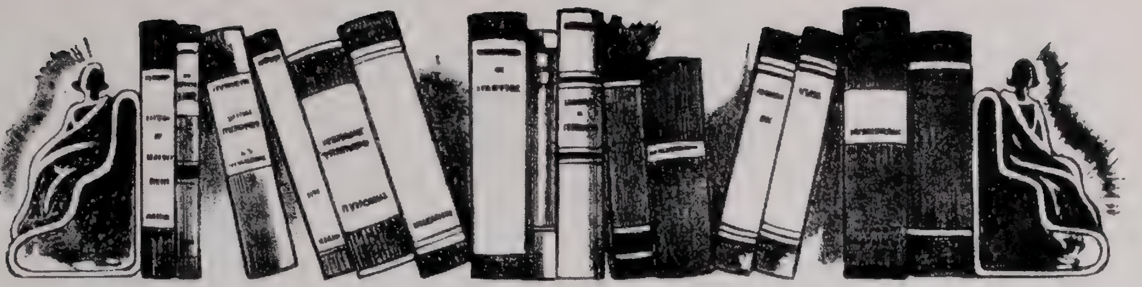
*Dr. Richard Carter, born in Virginia in 1786, medical practitioner and author of Valuable Vegetable Medical Prescriptions for the cure of All Nervous and Putrid Disorders, and also of A Valuable, Vegetable, Medical Prescription, with a table of Detergent and Corroborant Medicines to Suit the Treatment of the Different Certificates.

**Pickard and Buley: The Midwest Pioneer, His Ills, Cures, and Doctors, Henry Schuman, New York, 1946, p. 63.

Ills

So of doctors. They like fees no doubt — ought to like them; yet if they are brave and well-educated, the entire object of their lives is not fees. They, on the whole, desire to cure the sick; and — if they are good doctors, and the choice were fairly put to them — would rather cure their patient, and lose their fee, than kill him, and get it. — John Ruskin (1819-1900)



Book Reviews

Good books like good friends are few and chosen, the more select the more enjoyable. — Alcott

PEDIATRIC THERAPY, 2nd Edition — Harry S. Shirkey, M.D. (Editor) C. V. Mosby Company. $18.50.

This is an outstanding contribution to the care of infants and children, and Dr. Shirkey is to be complimented on the comprehensiveness and adequacy of the material covered. Admittedly, therapy is a treacherous domain; but for the most part the presentations are representative of current practices with enough explanatory text to make the discussions meaningful.

To attempt to critically review this prodigious text of 1223 pages would not be either practical or pertinent. It is not too difficult to find an occasional approach which doesn't meet with approval; but more remarkable is the fact that so much has been covered so well. It would seem best to leave it to the individual reader to find his points of disagreement.

A preface which contains the statement "complete treatment of the child is encouraged, and consideration is given to all those who contribute to his more complete care" shows immediate promise of a most ambitious undertaking. It is a tribute to the editor that he has organized the material so that this objective is sustained throughout the book.

The thoroughness of the coverage is such that the practicing physician will find this to be of great assistance in defining a therapeutic approach to a particular problem. For the most part the various editors have been most direct in their treatment providing an immediate practical approach for the interested physician. The intern and resident should find this compendium of pediatric therapy an essential companion as they enlarge their experiences in pediatric care.

The book is well-organized, illustrations are profusely used and the writing is, with few exceptions, concise and readable. My main concern is the ambitiousness of the undertaking with the inevitable necessity to compromise some of the subject matter. However, in contrast with other texts of similar content, Dr. Shirkey's book combines both adequacy and comprehensiveness in one volume and is highly recommended to all physicians who have a responsibility for the care of children.

Charles A. Branthaver, M.D.
Minneapolis, Minnesota

THERAPEUTIC RADIOLOGY — RATIONALE, TECHNIQUE, RESULTS — by William F. Moss, M.D., The C. V. Mosby Company, St. Louis, Mo., Second edition, 514 pages $15.00.

This is a completely revised edition of a well written concise textbook. The first edition was well appreciated by its users. This edition is brought up to present day knowledge and concept of the megavoltage therapy. It describes in necessary detail different cancers and their therapeutic management with particular application to radiotherapy.

A new chapter is added dealing with combination of radiotherapy and surgery. There is increasing interest among radiotherapists and surgeons about preoperative radiation with the hope of improving control of the primary cancer.

This book is recommended to radiology residents and radiotherapists as a guideline for cancer management. It is concise but contains all the pertinent facts for a good cancer radiotherapy. Other physicians may use it to familiarize themselves with the radiotherapeutic management of the cancer and acquire more knowledge of the effects of ionizing radiation on malignant growth as well as healthy tissues.

Arnolds Veinbergs, M.D.
Minneapolis, Minnesota

PERIPHERAL VASCULAR DISEASES — Travis Winsor and Chester Hyman, Lea & Febiger, Philadelphia, Copyright 1965.

This monograph has twenty-five small chapters dealing with the various phases of peripheral vascular diseases and includes some studies pertaining to peripheral fluids and lymph formation. It discusses arthritis, collagen disease, arterial aneurysms and fistulas, and the neurovascular syndrome of the upper extremities.

It is well bound and nicely printed. The index is not extensive but is adequate. The book is worth a place in the library of one who is interested in peripheral vascular diseases.

Carl O. Rice, M.D.
Minneapolis, Minnesota

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no unplanned pregnancies

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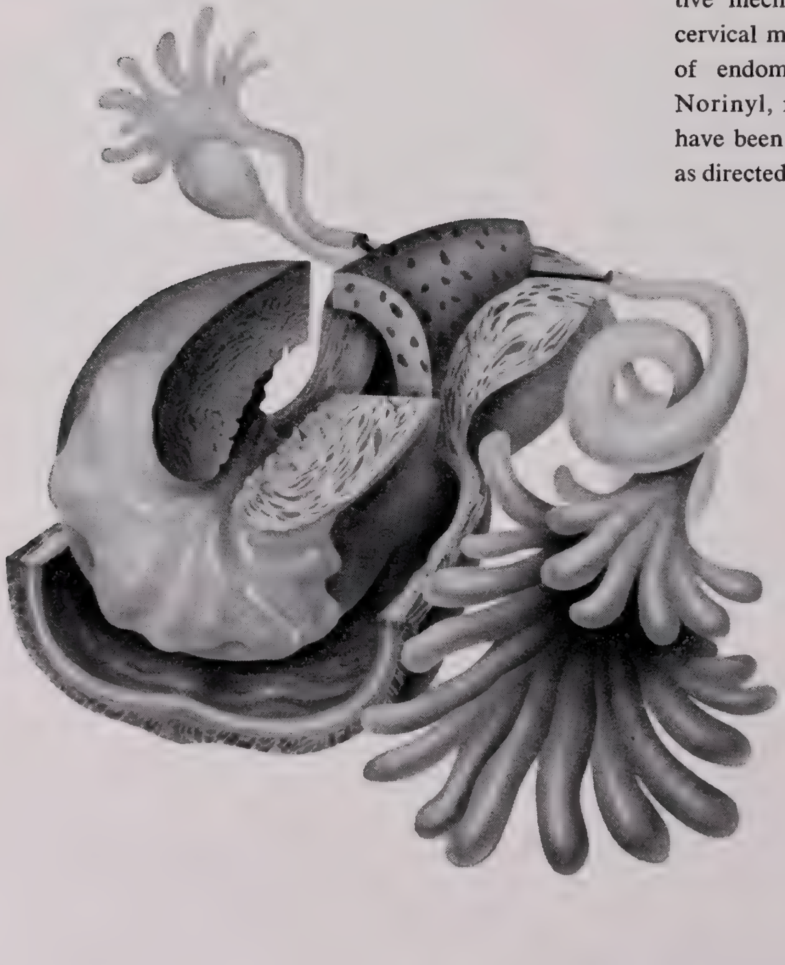

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no confusion about dosage

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Contraindications: Thrombophlebitis or pulmonary embolism (current or past). Existing evidence does not support a causal relationship between use of Norinyl and development of thromboembolism. While a study which was conducted does not resolve definitively the possible etiologic relationship between progestational agents and intravascular clotting, it tends to confirm the findings of the Ad Hoc Advisory Committee appointed by the Food and Drug Administration to review this possibility. Cardiac, renal or hepatic dysfunction. Carcinoma of the breast or genital tract. Patients with a history of psychic depression should be carefully studied and the drug discontinued if depression recurs to marked degree. Patients with a history of cerebral vascular accident.

Warning: Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Precautions: By May 1963, experience with norethindrone 2 mg.—mestranol 0.1 mg. had extended over 24 months. Through miscalculation, omission or error in taking the recommended dosage of Norinyl, pregnancy may result. If regular menses fail to appear and treatment schedule has not been adhered to, or if patient misses two menstrual periods, possibility of pregnancy should be resolved before resuming Norinyl. If pregnancy is established, Norinyl should be discontinued during period of gestation since virilization of the female fetus has been reported with oral use of progestational agents or estrogen. When lactation is desired, withhold Norinyl until nursing needs are established. Existing uterine fibroids may increase in size. In metabolic or endocrine disorders, careful clinical preevaluation is indicated. A few patients without evidence of hyperthyroidism had elevated serum protein-bound iodine levels, which in the light of present knowledge, does not necessarily imply hyperthyroidism. Protein-bound iodine increased following estrogen administration. Bromsulphalein retention has occurred in up to 25% of patients without evidence of hepatic dysfunction. Studies from 24-hour urine collections have shown an increase in aldosterone and 17-ketosteroids and decrease in 17-hydroxycorticoid levels. Thus, Norinyl should be discontinued prior to and during thyroid, liver or adrenal function tests. Because progestational agents may cause fluid retention, conditions such as epilepsy, migraine and asthma require careful observation. Thus far no deleterious effect on pituitary, ovarian or adrenal function has been noted; however, long-range possible effect on these and other organs must await more prolonged observation. Norinyl should be used with caution in patients with bone, renal or any disease involving calcium or phosphorus metabolism.

Side Effects: Intermenstrual bleeding; amenorrhea; symptoms resembling early pregnancy, such as nausea, breast engorgement or enlargement, chloasma and minor degree of fluid retention (if these should occur and patient has not strictly adhered to medication plan, she should be tested for pregnancy); weight gain; subjective complaints such as headache, dizziness, nervousness, irritability; in a few patients libido was increased. In a total of 3,090 patients, 2.2% discontinued medication because of nausea.

NOTE: See sections on contraindications and precautions for possible side effects on other organ systems.

Dosage and Administration: One Norinyl tablet orally for 20 days, commencing on day 5 through and including day 24 of the menstrual cycle. (Day 1 is the first day of menstrual bleeding.)

Availability: Dispensers of 20 and 60 tablets; bottles of 100.

References: **1.** Council on Drugs. JAMA 187:664 (Feb. 29) 1964. **2.** Brvans, F. E.: Canad Med Ass J 92:287 (Feb. 6) 1965. **3.** Goldzieher, J. W.: Med Clin N Amer 48:529 (Mar.) 1964. **4.** Cohen, M. R.: Paper presented at Symposium on Low-Dosage Oral Contraception, Palo Alto, Calif., July 15, 1965. Reported in Med Sci 16:26 (Nov.) 1965. **5.** Hammond, D. O.: Ibid. **6.** Rice-Wray, E., Goldzieher, J. W., and Aranda-Rosell, A.: Fertil Steril 14:402 (Jul.-Aug.) 1963. **7.** Goldzieher, J. W., Moses, L. E., and Ellis, L. T.: JAMA 180:359 (May 5) 1962. **8.** Kempers, R. D.: GP 29:88 (Jan.) 1964. **9.** Tyler, E. T.: JAMA 187:562 (Feb. 22) 1964. **10.** Rudel, H. W., Martinez-Manautou, J., and Maqueo-Topete, M.: Fertil Steril 16:158 (Mar.-Apr.) 1965. **11.** Flowers, C. E., Jr.: N Carolina Med J 25:139 (Apr.) 1964. **12.** Goldzieher, J. W.: Appl Ther 6:503 (June) 1964. **13.** The Control of Fertility. Report adopted by the Committee on Human Reproduction of the American Medical Association. JAMA 194:462 (Oct. 25) 1965. **14.** Flowers, C. E., Jr.: JAMA 188:1115 (June 29) 1964. **15.** Merritt, R. I.: Appl Ther 6:427 (May) 1964. **16.** Newland, D. O.: Paper presented at Symposium on Low-Dosage Oral Contraception, Palo Alto, Calif., July 15, 1965. Reported in Med Sci 16:26 (Nov.) 1965.

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Special Article

A Comparative Study on Selected Variables of Atopic and Non-Atopic Institutionalized Juvenile Delinquent Boys

ELMER M. RUSTEN, M.D.
E. MICHAEL RUSTEN, M.A.
Minneapolis, Minnesota

THE PURPOSE OF this study was to compare atopic* and non-atopic institutionalized juvenile delinquent boys on selected variables. There have been a number of studies made on the personality characteristics of atopic individuals. Characteristics reported include above average intelligence,[1,2,3] hostility,[4,5,6] resentment[3,6,7] aggression which is often suppressed,[1,8] and disrespect for the law.[6] Some studies[8,9,10] reported major sexual problems, whereas others[6,11] reported either only minor sexual disturbances or none. Allergics tended to be dissatisfied with their family life, to alienate their friends, to be cynical, irritable and grouchy, with no compensation techniques for their feelings of inferiority.[6]

This study first sought to determine whether there was a higher incidence of atopy among juvenile delinquent boys than in the general populace. Secondly, it also sought to investigate the relationship of atopy to race, intelligence, and type of committing offense among atopic and non-atopic institutionalized delinquents.

Procedure

The 322 boys who were inmates of the State Training School for Boys, Red Wing, Minnesota, as of midnight June 30, 1964, were the subject of the study. They ranged in age from thirteen to eighteen. The hospital records were consulted to determine which inmates had a history of atopic disease. The race, intelligence quotient, and type of offense were determined from other institutional records.

Results

Table 1 shows the incidence of atopy among the subjects. Ninety-nine or 30.7 per cent showed a history of some atopic disease.

Table 2 shows the breakdown of the atopic diseases found among the subjects. Seasonal

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*See Test Your Word Score Page 1411.

Continued

pollenosis had the highest frequency of 14.0 per cent; atopic dermatitis occurred in 5.9 per cent, while bronchial asthma and vasomotor rhinitis both had frequencies of 4.7 per cent.

Previous studies have sought to investigate the incidence of allergic diseases among the general population. Those reported since 1930 are found in Table 3. In 1930 Piness and Miller[12] reported the incidence of seasonal pollenosis in the population of two Arizona towns. In a town of 3000 population 4.4 per cent had histories of seasonal pollenosis, while in a town of 1000 the percentage was 3.0. In 1931 Rowe[13] made a study of 400 unselected students and nurses. Of these 35 per cent had a history of probable allergy. In 1934 Vaughan,[14] in a survey of an entire community of 508 individuals at Clover, Virginia, classified allergies as major and minor. Minor allergies were defined as minor episodic allergic manifestations due to contact with an allergen. The symptoms of minor allergies are transient and are relieved by avoiding the exciting allergens such as house dust, cosmetics, and offending fumes. Asthma and seasonal pollenosis were not included in this category. Vaughan found 10.8 per cent of the population to have major allergies and 48.1 per cent to have minor ones. Jimenez[15] investigated 7000 entering students at Michigan State University and found 35.0 per cent to be allergic. In 1937 Pipes[16] included 700 persons in a survey in and about Baton Rouge, Louisiana. Included in this study were secondary school children and students at Louisiana State University. Of these, 13.6 per cent were found to have major allergies and 35.8 per cent minor allergies. Service[17] in 1939 investigated 3141 persons in Colorado Springs, Colorado. Of these 22.6 per cent had a history of major allergy. Bernton[18] in 1957 made a survey of allergic disease among a prison population of 1500 in Washington, D.C. Of these 11.3 per cent had a major allergy while 11.7 per cent had a minor allergy. In a study in 1958 of 1225 children in a pediatric group practice in Tennessee, Crook, Harrison, and Stanley[19] found 14 per cent to be allergic and an additional 18 per cent to be probably allergic. Appel, Szanton, and Rapaport[20] in a survey of 6036 children found that over 23 per cent had one or more major allergies. In comparison with these studies the current investigation found 30.7 per cent of the subjects to be atopic.

TABLE 1
Incidence of Atopy Among Institutionalized Juvenile Delinquent Boys

Group	No.	%
Atopic	99	30.7
Non-atopic	223	69.3
Total	322	100.0

TABLE 2
Incidence of Atopic Diseases Among Institutionalized Juvenile Delinquent Boys

Atopic Disease	No.*	%
Seasonal pollenosis	45	14.0
Atopic dermatitis	19	5.9
Bronchial asthma	15	4.7
Vasomotor rhinitis	15	4.7
Urticaria	13	4.0
Sick headaches	9	2.8

*Some boys had more than one atopic disease.

The incidence of atopy according to race is found in Table 4. Approximately 30.5 per cent of the whites were found to be atopic, compared to 47.6 per cent of the Negroes and 21.4 per cent of the American Indians. However, the number of Negroes and American Indians included in the study was too small to draw any firm conclusions from the data.

The intelligence estimates of the two groups are compared in Table 5. The atopic subjects had slightly higher intelligence estimates than the non-atopic. Three-fourths of the atopic group had intelligence estimates of average or higher, while this was true of only slightly over two thirds of the non-atopic group. This substantiates the findings of the previously listed studies.

The types of crimes for which the atopic and non-atopic subjects were committed to the institution are recorded in Table 6. An identical percentage of 64.6 per cent of atopic and non-atopic subjects had committed crimes against property. However, twice as high a percentage of atopic subjects had committed crimes against persons as compared to non-atopic subjects. Approxi-

TABLE 3
Incidence of Atopy as Reported in Other Studies

Year	Authors	Locality or Group	No.	Per Cent of Seasonal Pollen-osis	Per Cent of Bronchial Asthma	Per Cent of Major Allergy	Per Cent of Minor Allergy
1930	Piness and Miller	Arizona	3000	4.4			
1930	Piness and Miller	Arizona	1000	3.0			
1931	Rowe	California	400			35.0	
1934	Vaughan	Virginia	508	5.3	3.3	10.8	48.1
1934	Jimenez	Michigan	7000			35.0	
1937	Pipes	Louisiana	700	3.6	5.0	13.6	35.8
1939	Service	Colorado	3141	10.1	3.6	22.6	
1957	Bernton	Prison*	1500	1.8	4.4	11.3	11.7
1958	Crook et al.	Children**	1225	2.2	4.7	14.3	
1961	Appel et al.	Children†	6036			23.7	
1964	Rusten and Rusten	Training School‡	322	14.0	4.7	30.7	

*Washington, D. C.
**Tennessee.
†Northeastern United States and Montreal.
‡Red Wing, Minnesota.

TABLE 4
Incidence of Atopy According to Race Among Institutionalized Juvenile Delinquent Boys

Group	White No.	White %	Negro No.	Negro %	American Indian No.	American Indian %	Mexican No.	Mexican %	Total No.	Total %
Atopic	83	30.5	10	47.6	6	21.4	0	0.0	99	30.7
Non-Atopic	189	69.5	11	52.4	22	78.6	1	100.0	223	69.3
Total	272	100.0	21	100.0	28	100.0	1	100.0	322	100.0

TABLE 5
Intelligence Estimates of Atopic and Non-Atopic Institutionalized Juvenile Delinquent Boys

Intelligence	Atopic No.	Atopic %	Non-Atopic No.	Non-Atopic %	Total No.	Total %
Superior	4	4.0	4	1.8	8	2.5
Bright normal	9	9.1	20	9.0	29	9.0
Average	62	62.7	128	57.4	190	59.0
Dull normal	20	20.2	55	24.7	75	23.3
Borderline	4	4.0	11	4.9	15	4.7
Defective	0	0.0	3	1.4	3	.9
Unknown	0	0.0	1	.4	1	.3
Illiterate	0	0.0	1	.4	1	.3
Total	99	100.0	223	100.0	322	100.0

Continued

TABLE 6
Number and Percentage of Atopic and Non-Atopic Juvenile Delinquent Boys Committing Different Types of Offenses

Type of Offense	Atopic		Non-Atopic		Total	
	No.	%	No.	%	No.	%
Crimes against persons	16	16.2	18	8.1	34	10.6
Crimes against property	64	64.6	144	64.6	208	64.6
Crimes against morals, chastity, and decency	0	0.0	5	2.2	5	1.6
Crimes against justice	41	41.4	73	32.9	114	35.1
Total*	121		240		361	

*Some boys committed crimes in more than one category.

TABLE 7
Type of Committing Offenses of Atopic and Non-Atopic Institutionalized Juvenile Delinquent Boys

Type of Offense	Atopic		Non-Atopic		Total	
	No.	%	No.	%	No.	%
Crimes Against Persons						
Robbery	9	9.1	7	3.1	16	5.0
Assault	5	5.0	8	3.6	13	4.0
Purse-Snatching	2	2.0	1	1.4	3	.9
Carrying a deadly weapon	0	0.0	1	.4	1	.3
Manslaughter	0	0.0	1	.4	1	.3
Crimes Against Property						
Auto theft	33	33.3	67	30.0	100	31.1
Burglary	8	8.1	37	16.6	45	13.9
Theft	12	12.1	24	10.8	36	11.2
Breaking and entering	10	10.1	22	9.9	32	9.9
Larceny	2	2.0	6	2.7	8	2.3
Vandalism	3	3.0	3	1.3	6	1.9
Shoplifting	2	2.0	3	1.3	5	1.6
Arson	3	3.0	1	.4	4	1.2
Forgery	1	1.0	1	.4	2	.6
Car prowling	0	0.0	1	.4	1	.3
Checking on bank without funds	0	0.0	1	.4	1	.3
Crossing state line in stolen car	0	0.0	1	.4	1	.3
Possession of stolen car	0	0.0	1	.4	1	.3
Possession of stolen property	0	0.0	1	.4	1	.3
Crimes Against Morals, Chastity, and Decency						
Sodomy	0	0.0	3	1.3	3	.9
Carnal knowledge	0	0.0	1	.4	1	.3
Indecent assault	0	0.0	1	.4	1	.3
Rape	0	0.0	1	.4	1	.3
Crimes Against Justice						
Run-away	22	22.2	49	22.0	71	22.0
Truancy	7	7.1	11	4.9	18	5.6
Absenting	4	4.0	10	4.5	14	4.3
Incorrigibility	6	6.1	8	3.6	14	4.3
Curfew	3	3.0	2	.9	5	1.6
Violation of liquor laws	3	3.0	0	0.0	3	.9
Disorderly conduct	1	1.0	1	.4	2	.6
Leaving state	0	0.0	1	.4	1	.3
Sniffing glue	0	0.0	1	.4	1	.3
Traffic offense	0	0.0	1	.4	1	.3

mately 16.2 per cent of the atopic group had committed this type of crime as opposed to only 8.1 per cent of the non-atopic group. A higher percentage of atopics than non-atopics had also committed crimes against justice. The percentage for the the atopic group was 41.4 per cent as compared to only 32.9 per cent for the non-atopic group. On the other hand, all five of the subjects committing crimes against morals, chastity and decency were non-atopics.

Table 7 shows a breakdown of the actual crimes committed by the subjects. The greatest differences between atopics and non-atopics were found in the crimes of robbery and burglary. Of the atopic individuals 9.1 per cent had committed robbery as opposed to only 3.1 per cent of the non-atopics. On the other hand, 16.1 per cent of the non-atopics had committed burglary as compared to only 8.1 per cent of the atopics. The atopics thus tended to commit crimes against persons.

Summary and Conclusions

The study sought to investigate the incidence of atopy among institutionalized juvenile delinquent boys and to determine the relationship of atopic disease to race, intelligence, and type of committing offense. The 322 boys who were inmates of the State Training School for Boys, Red Wing, Minnesota, as of June 30, 1964, served as subjects for the study. The results were as follows:

1. The incidence of atopy among the institutionalized juvenile delinquents studied was 30.7 per cent. This was medial of the percentages in the general population as reported by eight authors.
2. There was a higher incidence of atopy among Negroes than whites.
3. The intelligence estimates of the atopics were slightly higher than those of non-atopics.
4. A higher percentage of atopics than non-atopics were committed to the institution for crimes against persons and justice. No atopics were committed for crimes against morals, chastity, or decency.

Acknowledgment

It is the authors' privilege to record their appreciation and thanks to Nathan Mandel, Ph.D., Director of Research, Minnesota Department of Corrections; to Mr. Delbert Leaf, Superintendent, State Training School for Boys, Minnesota Department of Corrections; and to the several members of their staffs for the cooperation and help which has made this study possible.

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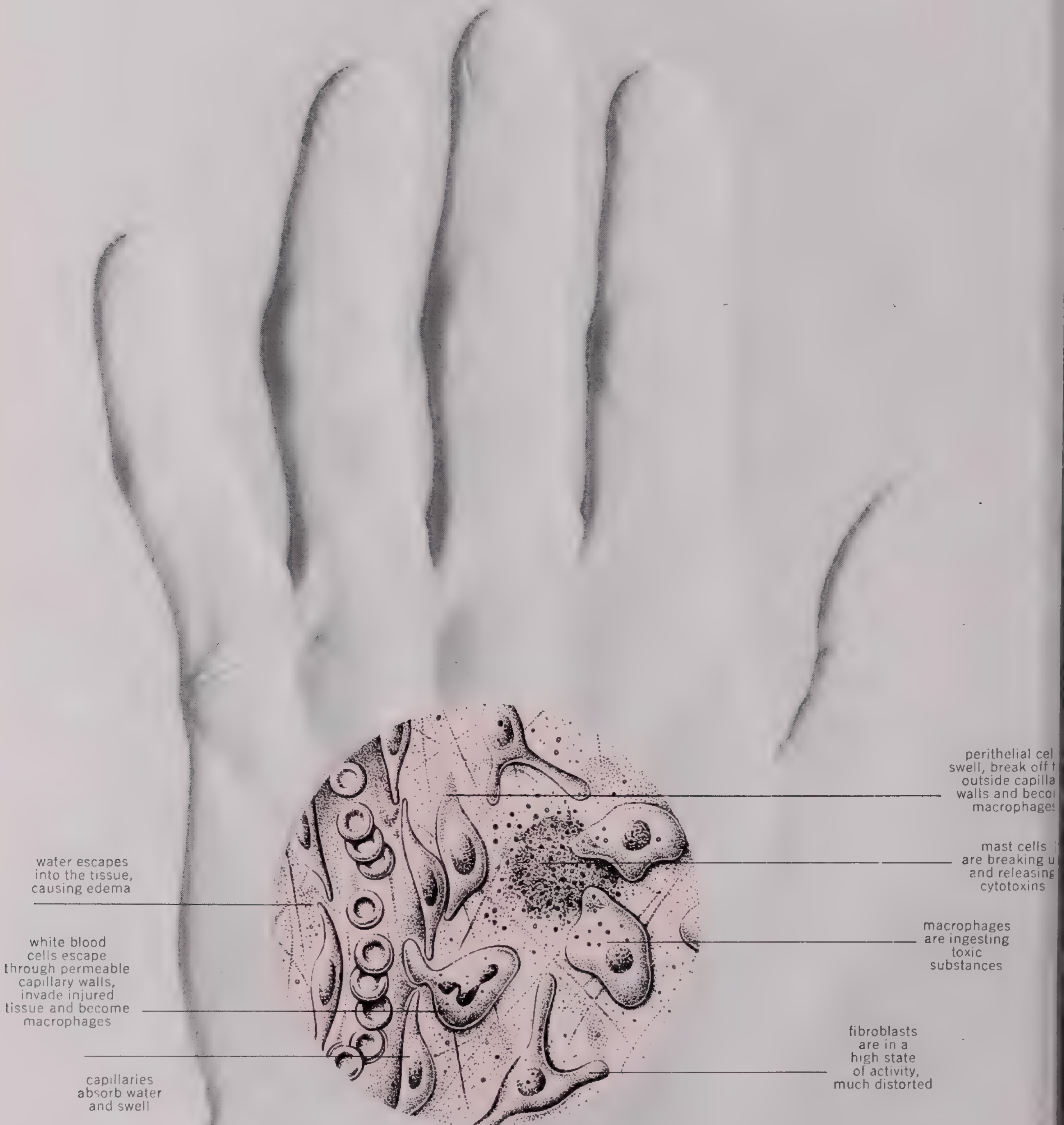
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In Memoriam

Be still prepared for death: and death or life shall thereby be sweeter.
— Shakespeare

GEORGE B. EUSTERMAN, M.D.

Dr. George B. Eusterman, Sr., 84, a member of the staff of the Mayo Clinic, died July 11, in Rochester. He was born in Lewiston and received his degree of doctor of medicine at the University of Minnesota.

He was certified as a specialist in internal medicine by the American Board of Internal Medicine in 1940 and became a member of the examining board in the subspecialty of gastroenterology. He was an emeritus member of the American Medical Association, a fellow of the American College of Physicians, member of the Central Society for Clinical Research, the Central Interuban Clinical Club, the Minnesota Society of Internal Medicine and a corresponding member of a number of foreign scientific organizations.

In 1921 Dr. Eusterman was president of the American Gastroenterological Association, and in 1946 this organization awarded him the Friedenwald Medal for outstanding work in gastroenterology. He was the author of approximately 150 papers dealing with diseases of the upper part of the digestive tract and metabolism and nutrition. He was awarded a certificate of merit by the University of Minnesota, a certificate of Master of the American College of Physicians and was a 50 Club and associate member of the Minnesota State Medical Association in addition to being a member of the Zumbro Valley Medical Society.

He is survived by his wife, three daughters and two sons, Dr. George Eusterman, Jr. of Great Falls, Montana, and Dr. Joseph H. Eusterman of Albany, Oregon.

GEORGE M. TANGEN, M.D.

Dr. George M. Tangen, 68, Taylors Falls physician, died July 25, of a heart attack while working in his yard. Born in Duluth, he received his medical degree at the University of Minnesota Medical School. Dr. Tangen practiced in Canby for fifteen years before moving to Minneapolis in 1940.

He was a member of the medical staffs of Abbott and St. Barnabas Hospitals, and an associate professor in the Department of Otolaryngology at the University of Minnesota Hospitals. Dr. Tangen was a member of the American Medical Association and Hennepin County Medical Society and an associate member of the Minnesota State Medical Association.

He is survived by his wife, a daughter and a son, Dr. George V. Tangen of Minneapolis.

WILLIS H. THOMPSON, M.D.

Dr. Willis H. Thompson, 66, assistant professor of pediatrics at the University of Minnesota, died July 24. Born in New Auburn, Wisconsin, Dr. Thompson received his medical degree from the University of Minnesota Medical School.

He was on the staffs of St. Mary's, Abbott and Swedish Hospitals and a member of the Hennepin County Medical Society, American Medical Association, American Society of Pediatrics, Northwestern Pediatric Society and an associate member of the Minnesota State Medical Association.

He is survived by his wife and six sons.

FREDERICK E. HILL, M.D.

Dr. Frederick E. Hill, 78, a former Duluth physician who practiced in the city for forty-four years, died July 19, in Riverside, California. Born in Trenton, New Jersey, Dr. Hill was a graduate of the University of Pennsylvania Medical School.

A member of the staffs of St. Luke's and St. Mary's Hospitals, Dr. Hill was also a member of the St. Louis County Medical Society, American Medical Association and a 50 Club and associate member of the Minnesota State Medical Association.

He is survived by his wife and two daughters.

JOHN A. SWANSON, M.D.

Dr. John A. Swanson, 77, St. Paul physician for twenty-eight years, died August 16 after an illness of twelve years. Born in Gull River, Minnesota, he obtained his medical degree at the Valparaiso University in Indiana and the Louisville University Medical School.

He was a member of the Ramsey County Medical Society, American Medical Association, East Side Post No. 358 American Legion and an associate member of the Minnesota State Medical Association.

He is survived by his wife.

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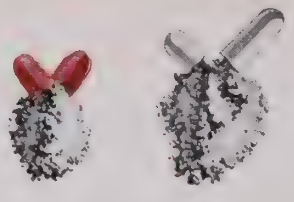

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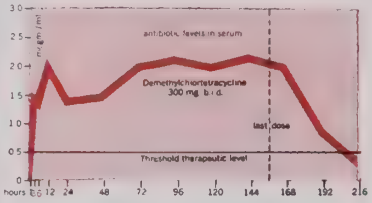

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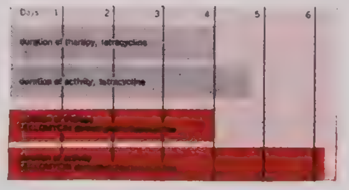

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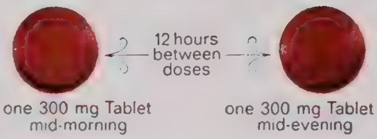

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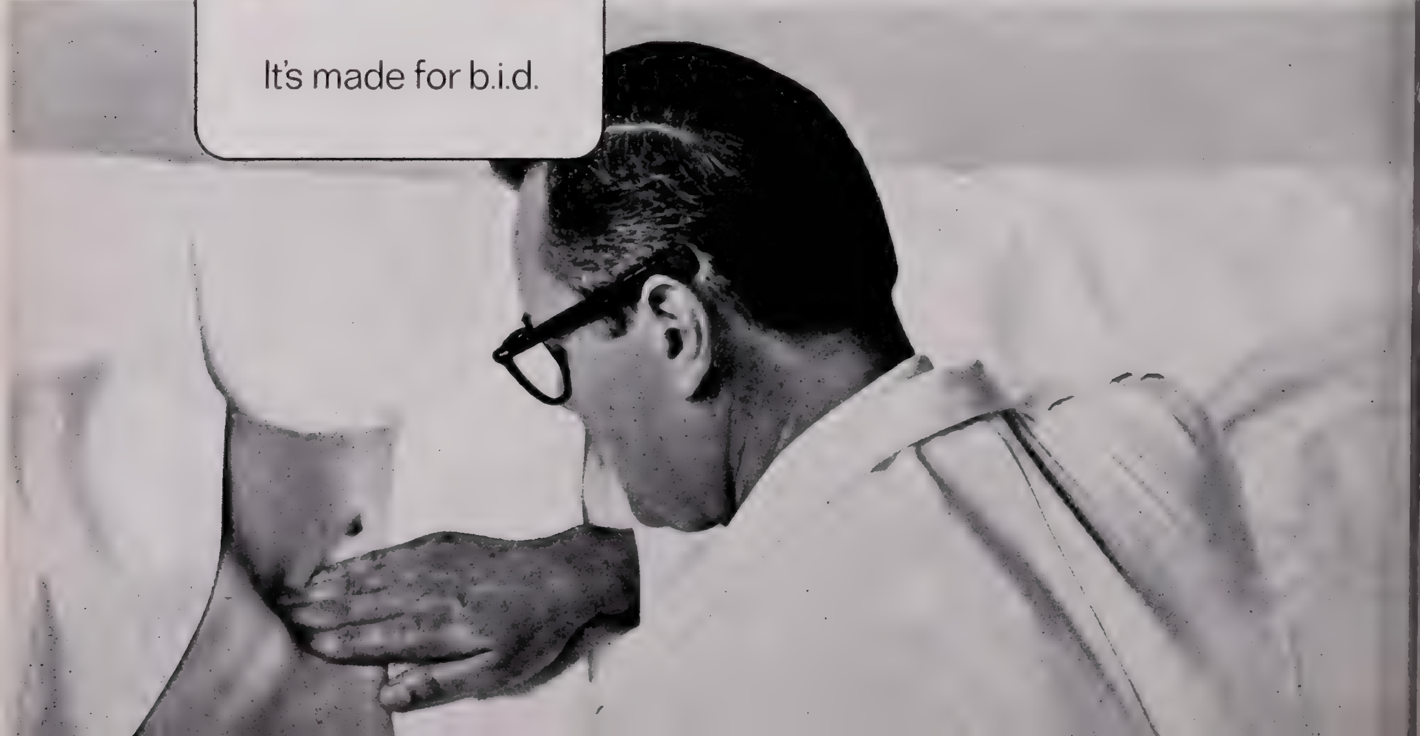
Contraindication—History of hypersensitivity to demethylchlortetracycline.
Warning—In renal impairment, usual doses may lead to excessive systemic accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated and, if therapy is prolonged, serum level determinations may be advisable. A photodynamic reaction to natural or artificial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sunburn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photoallergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug at the first evidence of skin discomfort.
Precautions and Side Effects—Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken. Use of demethylchlortetracycline during tooth development (last trimester of pregnancy, neonatal period and early childhood) may cause discoloration of the teeth (yellow-grey-brownish). This effect occurs mostly during long-term use but has also been observed in short treatment courses. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment. Side reactions include glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis and dermatitis. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy. Anaphylactoid reactions have been reported.

Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products.

Capsules: 150 mg; *Tablets:* film coated, 300 mg, 150 mg, and 75 mg of demethylchlortetracycline HCl.



Medicine and Religion

Ethical Implications of Therapeutic Abortion

All ethical questions ultimately depend for answer upon the metaphysical question of the nature of values. Are values intrinsically good? Or are they extrinsically good only according to the situation in which they find themselves? Is life a value that has absolute goodness regardless of the circumstances or context in which a particular life may be found? Or is life good relative to a community of persons, things, and events which together give it value? The question of therapeutic abortion rests upon the solution of the question of value.

Usually this question is put in the form of a dilemma which is as logically false as it is practically inoperative. On one horn we find a normative, prescriptive position which may be defined in terms of either natural reason or Biblicistic rules of behavior. We may say reason assures us that human life is inviolable or the Bible says: Thou shalt not kill. Such a stand tends to become legalistic and absolutistic. Persons may be broken for principles, canons of justice may be served, but such decisions lack love. On the other horn we find a relativistic, descriptive position which says abortion is permissible if desired. This stand tends to become antinomian.* In the name of love it violates justice because in its permissiveness it becomes arbitrary. What it calls love in justification of its relativism is not really love at all. It is egocentric indulgence.

Instead of the simplistic logic of this dilemma we must look at our problem as if we had a spectrum of options, not just blacks and whites but many colors and shades. We must avoid both extremes of loveless legalism and reckless relativism. Just as the justice of absolutism ultimately fails to respect people and hence fails to do justice, so the indulgence of relativism ultimately fails to love people and leads to a fascist manipulation of life according to arbitrary standards. But if, because the situation must be considered, we reject the absolutist norm that no therapeutic abortion is licit, we must not fall into the trap of thinking the situation will tell us what to do. This is what many advocates of the so-called new morality or situational ethics do. The result is crypto-antinomianism.

It is here that our sense of value is brought to bear. The Judeo-Christian belief in the Spirit of God brings a new dimension into the discussion. Because the Spirit breathes life into man he is a creature radically different from all other creatures in quality. Man is a spirit with an eternal destiny. The breeding he gets from genetic formulae may control his mind and his pancreas and his cardiac valves, but it cannot control his spirit. Therefore it is not the situation that will determine our course of action, nor will it be an *a priori* norm, but rather it will be the Spirit speaking to us in faith as members of a community which knows itself to be the family of God destined to glorify God by serving men.

Many factors enter into the decision. First there is the guidance of the Spirit. Then there is the free, personal, responsible, and faithful choice of the individual. Doctors and patients cannot shift responsibility for decision

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*See Test Your Word Score, Page 1411.

Continued

to each other or to an impersonal legal status; they must bear each other's burdens and decide with God whether the persons involved in the crisis are redeemable.

If this is the case we have an absolute in God to direct us; but his direction is never so rigid that it breaks people. There may be occasions when therapeutic abortion will be necessary, but life is still inviolable and neither mother nor fetus has preference. In a split-second crisis a doctor may have to make a choice in which he lets one person die while saving another. He cannot avoid sharing in the guilt of having to choose what he considers the lesser of two evils. He chooses bravely, knowing that his action is forgiven so long as it is done faithfully under the guidance of the Spirit and with his brothers in community. We must simply agonize in prayer to discern the guidance of the Spirit in each moment of decision.

What shall a doctor or patient do in case of rape or incest or pre-natal malformation or extra-marital pregnancy? If God is to be glorified and persons are to be served and if we are not simply to satisfy local situations or arbitrary norms, then we must ask if the persons involved are redeemable. Can we guide people caught in unwanted or dangerous pregnancy to accept their situation and creatively redeem it? Can forgiveness be brought to bear? Can the aid of the community be provided (including the technical skill of the doctor)? These questions give room for the grace of God to operate in a sinful situation. Unless we proceed on the basis of this faith we will fall into the cynicism which says abortions should be legalized because if they are not, people will seek illegal means, and it is better to have an abortion done safely than by quacks. With such a desperate argument one could legalize all kinds of murder.

It is too easy to say that abortions should be permitted because the fetus is not yet a person. The time when a fertilized ovum becomes a person cannot really be determined without being arbitrary. One can only say that we are all on our way to becoming persons from the moment of implantation until the moment of resurrection. Life begins at the juncture under the Spirit of three persons, father, mother, and child.

An extra-marital pregnancy need not destroy a marriage if there if forgiveness. A marriage threatened by extra-marital or unwanted pregnancy is not going to be strengthened by running away from the problem or blotting it out with a surgical sponge. A threat of suicide calls for more serious counselling but does not justify abortion. A new mouth to feed need not bring economic disaster if there is community concern. There are better ways of population control. Even pregnancies due to rape need not be terminated when it is considered that the child has a right to live for God's glory and that forgiveness is possible here too. The possibility of deformity may be greatly regretted, but to what extent can such deformity be predicted and to what extent can it be corrected? Here are evils, which may or may not involve guilt, but these are evils that are redeemable and should be faced with saving faith. By too hasty indulgence which masquerades as love we rob God of his grace, the community of its responsibility for social welfare, and involved individuals of their need to face sin with confession. To believe in forgiveness means not only to accept a sinful situation even if it is painful or disgraceful, but also to transform courageously that situation and the people involved into a positive good.

It would seem on the basis of this thinking that the best approach to our problem would be to bring medical science into conversation with pastoral care so that what is done with the body can be done in harmony with what is done with the spirit of persons in the community of the church. All these considerations derive from the faith that the human person is a spirit with an eternal destiny. Naturally if you reduce man to a congeries of stimuli and responses the problem will be solved differently. If, as Julian Huxley says, man is a protoplasmic agglomerate on the way to becoming fertilizer, an animated tube that runs at both ends, one will simply decide on the basis of the need for fertilizer. But if man is a spirit, then he has both freedom and responsibility and must seek to serve God and persons.

Robert P. Roth, Ph.D.*
Minneapolis, Minnesota

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*Dean of the Graduate School Northwestern Lutheran Seminary.

Appliance Cures

When the Austrian professor of astronomy, Hell, made his magnets in the shape of various organs in order that they might have a definite curative effect on those organs, he was taking advantage not only of the mystery of magnetism for curative purposes, but also the suggestive influence of an especially shaped appliance. Shapes have had wonderful influence on the mind of man for good or ill. A kidney-shaped magnet or one in the form of the liver or the heart would create expectancy and provide suggestion more than just a magnet of ordinary shape.

Plasters, for instance, that are employed for the purpose of affecting the kidneys favorably at many times have been shaped like kidneys. It was a rare thing to examine a patient in a New York dispensary twenty-five years ago and not find a kidney-shaped plaster sticking firmly to his back.

A favorite remedial appliance when I was a boy, for I remember them hanging in sight in the windows of the drug stores of that time, were liver pads. These were pads of various shapes and sizes containing a variety of simples, hops,* gentian,** penny-royal† and the like, which were supposed to be very efficient in stimulating the liver.

The number of wonderful cures worked by these harmless applications was without end for a time and there was an abundance of testimonials to demonstrate the fact that they had made life worth living for a great many people after it had seemed clear for years that life could never be worth while again.

Such are the ways of men and women.‡

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*A vine, the dried cones of which are used as a tonic and soporific.
**A plant, the roots of which are used as a tonic and stomachic.
†A mint used as a culcifuge (a mosquito repellent).
‡Walsh, James: Cures, D. Appleton & Co., New York, 1924.

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Warning: Patients who experience dizziness, lightheadedness, or feelings of detachment on INDOCIN should be cautioned against operating motor vehicles, machinery, climbing ladders, etc. Use cautiously in patients with psychiatric disturbances, epilepsy, or parkinsonism.
Precautions and Adverse Reactions: Most commonly, headache, dizziness, lightheadedness, G.I. disturbances. The C.N.S. effects are often transient and frequently disappear with continued treatment or reduced dosage. The severity of these effects may occasionally require cessation of therapy. G.I. effects may be minimized by giving the drug with food or with antacids or immediately after meals. Ulceration of the stomach, duodenum, or small intestine has been reported and, in a few instances, severe bleeding with perforation and death. Gastrointestinal bleeding with no obvious ulcer formation has also been noted; INDOCIN should be discontinued if G.I. bleeding occurs. As a result of G.I. bleeding, some patients may manifest anemia, and for this reason periodic hemoglobin determinations are recommended. Rare reports of effects not definitely known to be attributable to INDOCIN include bleeding from the sigmoid colon (either from a diverticulum or without a known previous pathologic condition), perforation of preexisting sigmoid lesions (diverticulum, carcinoma), and hematuria. In other rare cases, a diagnosis of gastritis has been made while the drug was being given. One patient developed ulcerative colitis, and another, regional ileitis, while receiving INDOCIN; when the drug was given to patients with preexisting ulcerative colitis, there was an increase in abdominal pain. Infrequently observed side effects may include drowsiness, tinnitus, mental confusion, depression and other psychic disturbances, blurred vision, stomatitis, pruritus, edema, and hypersensitivity reactions. Slight BUN elevation, usually transient, has been seen in some patients, although the preponderance of evidence indicates that INDOCIN does not adversely affect renal function, even in patients with preexisting renal disease. Nevertheless, renal function should be checked periodically in patients on long-term therapy. Leukopenia has been seen in a few patients. Transient elevations in alkaline phosphatase, cephalin-cholesterol flocculation, and thymol turbidity tests have been observed in some patients and, rarely, elevations of SGOT values; the relationship of these changes to the drug, if any, has not been established. As with any new drug, patients should be followed carefully to detect unusual manifestations of drug sensitivity. Before prescribing or administering, read product circular with package or available on request.

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1. Schleif, R.H.: J.A.PH.A., 46:179,1957 *U.S. Pat. No. 3,062,714

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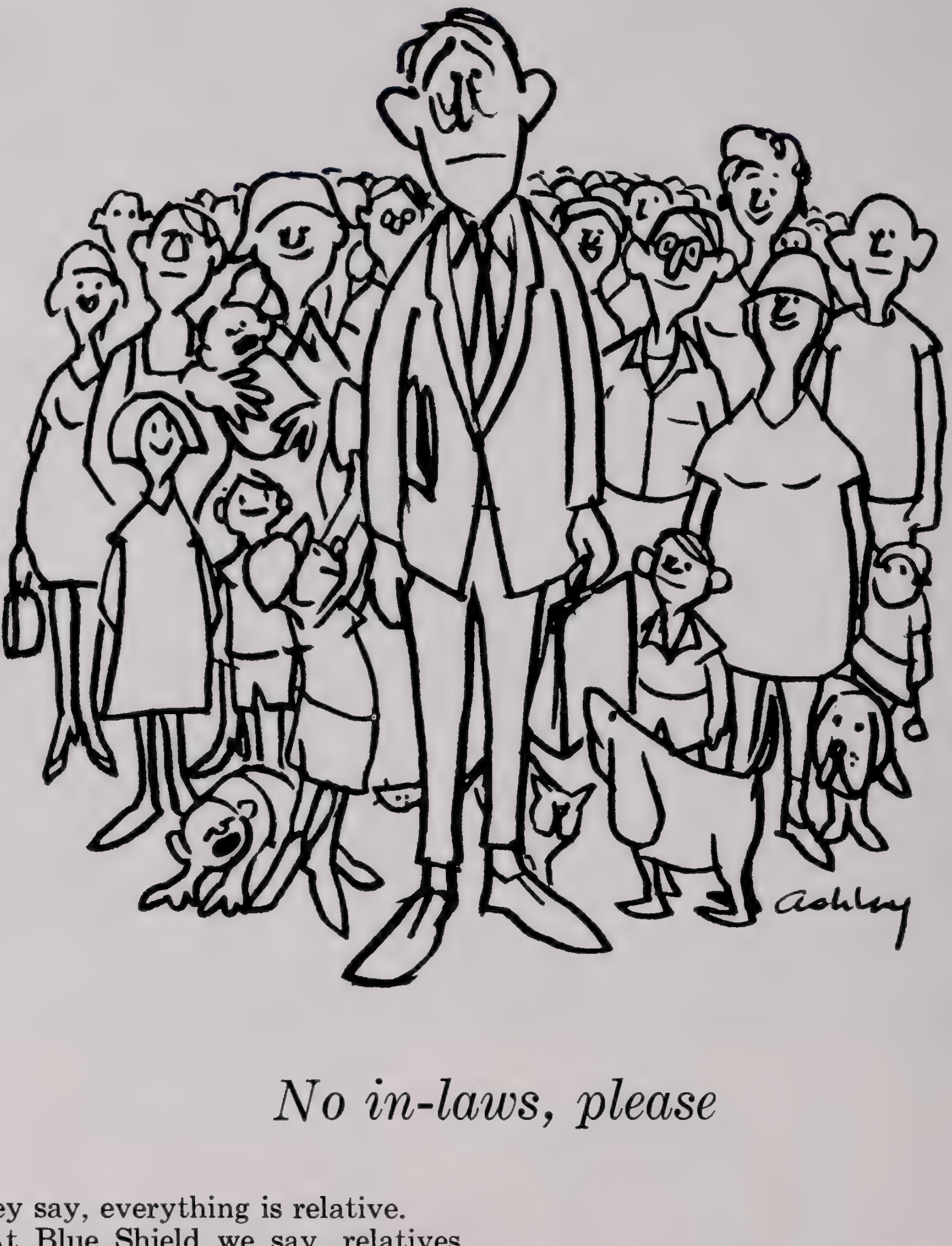

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Meetings and Announcements

My gems are falling away; but it is because God is making up his jewels. — Wolfe

SEPTEMBER

The Annual Fall Meeting of the Northwestern Pediatrics Society will be held on Friday, September 23, at the White Pine Inn, Bayport. Eldon Berglund, M.D. President.

Minnesota Society of X-ray Technologists Annual Meeting, September 30-October 1, Statler Hilton Hotel, St. Paul. Contact: Richard Board, R.T., 416 Marquette Bank Building, Minneapolis.

Second Annual Symposium on Kidney Disease sponsored by the Upper Midwest Chapter of the National Kidney Foundation, St. Paul Hilton Hotel, September 14. Contact: John M. Burns, M.D., 451 North Dunlap, St. Paul.

Scientific Meeting of the Minnesota Society of Anesthesiologists, September 23rd, Place to be determined. Contact: Van Lawrence, M.D., Mayo Clinic, Rochester.

Park Region District Medical Society, Alexandria — September meeting (date not set).

Scott-Carver Medical Society, Jordan — September 6, 7:30 p.m., Wagner's Colonial Club.

Zumbro Valley Medical Society, Rochester — September 7, 8.00 p.m., Mann Hall.

St. Louis County Medical Society, Duluth — September 8, Ex. Comm. at 6:00 p.m., regular meeting at 8:00 p.m., St. Mary's Hospital.

Camp Release District Medical Society, Montevideo — September 9, 6:30 p.m., Hunt Hotel

Wisconsin Society of OB & GYN, Marshfield, Wis. —September 9-10, Marshfield Clinic.

Minnesota-Dakota-Manitoba Orthopedic Society — September 9-10, Ambassador Motel, Minneapolis.

Medical Legal Conference, Rapid City — September 10, South Dakota.

Thirteenth Annual Internal Medicine Symposium — September 10, Iowa Methodist Hospital, Des Moines.

Minnesota Radiological Society, Brainerd Fall meeting — September 10-11, Rutger's Lodge.

Southwestern Minnesota Medical Society, Worthington, September 12, 7:00 p.m.

Twin City Urological Society, St. Paul — September 16, 6:00 p.m. Town & Country Club.

Nebraska Academy of General Practice — September 16-17, Cornhusker Hotel, Lincoln.

Iowa Chapter, American Academy of General Practice — Annual scientific sessions — September 18-19, Savery Hotel, Des Moines.

Blue Earth Valley Medical Society, Fairmont — September 21, Interlaken Golf Club, 6:30 p.m.

Wisconsin Academy of General Practice — September 25-27, Milwaukee.

Ramsey County Medical Society — September 26, 8:00 p.m., regular meeting, 15th floor, Lowry Medical Arts Building, St. Paul.

Range Medical Society — Ely, Executive and general meeting — September 27, following 7:00 p.m. dinner.

Dinner Meeting of Hennipin County Hospital Medical Staff, 6:30, September 26.

OCTOBER

Minnesota Society of Internal Medicine, St. Paul — October 17, 8:00 a.m.

Blue Earth Valley Medical Society, Interlaken Golf Club, Fairmont— October 19.

Twin City Urological Society, Town & Country Club, St. Paul — October 21, 6:00 p.m.

Quain & Ramstad Fall Clinic Conference, Bismarck, North Dakota — October 22.

Ramsey County Medical Society — October 31, 8:00 p.m. regular meeting, 15th floor Lowry Medical Arts Bldg., St. Paul.

Southwestern Minnesota Medical Society, Worthington — October 3, 7:00 p.m.

Nicollet-LeSueur County Medical Society, Holiday House, St. Peter — October 3, 6:30 p.m.

Scott-Carver County Medical Society, Wagner's Colonial Club, Jordan, — October 4, 7:30 p.m.

Hennepin County Academy of General Practice, Pick-Nicollet, Minneapolis — October 6, 6:00 p.m.

Brown County Medical Society, Dakota Hotel, New Ulm — October 11, 7:00 p.m.

Minnesota Academy of Medicine, Town & Country Club, St. Paul — October 12, 6:30 p.m.

St. Louis County Medical Society, Ex. Comm. at 6:00 p.m., regular meeting at 8:00 p.m., October 13, St. Luke's Hospital, Duluth.

Camp Release District Medical Society, Hunt Hotel, Montevideo — October 13.

Hennepin County Academy of General Practice, Athletic Club, Minneapolis — October 17, 6:00 p.m.

ANNOUNCEMENTS

Minnesota Obstetrical-Gynecological Society Meeting, December 3rd, Hennepin County General Hospital. Contact: Theodore Watson, M.D., 1261 Lowry Medical Arts Building, St. Paul.

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Physician's Diary

We take care of our health, we lay up money, we make our roof tight and our clothing sufficient, but who provides wisely that he shall not be wanting in the best property of all — friends? — Emerson

Dr. Raymond J. Jackman, head of the Section of Proctology of the Mayo Clinic, was named president-elect of the American Proctologic Society at its annual meeting in Cleveland.

* * *

Dr. Edward H. Rynearson and **Dr. Harold L. Mason,** members of the staff of the Mayo Clinic, have retired from the Mayo Clinic in Rochester.

* * *

The following physicians were inducted into Fellowship in the American College of Physicians: **Dr. Neil D. Nickerson** of Fairmont; **Drs. Robert B. Breitenbucher, Robert S. Eliot, Mark Hanson** and **William F. Nuessle** of Minneapolis; **Dr. George M. B. Hawley** of Red Wing: **Drs. Michael Dimaio, Donald J. Erickson, John A. Higgins, Carlos E. Harrison, John L. Magness, Frank J. Maher** and **Don C. Purnell** of Rochester; **Dr. James H. Kelly** of St. Cloud; and **Drs. Paul D. Redleaf, Francis B. Tiffany** and **John W. Yarbro** of St. Paul.

* * *

Dr. Wallace E. Mathews of Mankato recently received the Minnesota Academy of General Practice 1965 merit award. This award is given each year to the general practitioner who has done the most for the academy in the past year.

* * *

Dr. Leonard Lang of Minneapolis was recently honored by the students at the College of St. Thomas. An alumni award was presented to Dr. Lang on occasion of a dinner in his honor.

* * *

Dr. John B. Coleman of St. Paul is the new president-elect of the medical staff of Miller Hospital, and **Dr. Robert L. Merrick** has been named the first vice-president.

* * *

Mrs. W. A. Merritt, Rochester, was elected to a two-year term on the Board of Directors of the Woman's Auxiliary to the American Medical Association during the organization's 43rd annual convention.

* * *

Dr. Charles A. Neumeister of Minneapolis, is the new president of Blue Shield of Minnesota.

* * *

Dr. Harry E. Furgeson is the new president of the American Veterinary Medical Association.

* * *

Dr. Robert L. Hegrenes, Rivers Edge Clinic in Farmington, has been elected to active membership in the American Academy of General Practice.

* * *

Doctors Robert H. Feldt, Richard S. Sheldon, Ross J. Wood, and **Alan F. Hofmann** have been appointed to the staff of the Mayo Clinic, Rochester.

* * *

Dr. Edward M. Lafond has been elected chief-of-staff of the St. Cloud Hospital. Other officers elected were: **Dr. O. C. Phares,** vice chief-of-staff, and **Dr. J. W. Smith,** secretary.

* * *

NEW LOCATIONS: **Dr. Kenneth Covey** has left the Northwestern Clinic in Crookston to open a practice in Moorhead . . . **Dr. Dudley E. Wilkinson** has joined the staff at the Reserve Mining Co. dispensary in Silver Bay . . . **Dr. John Zapf** has become associated with **Doctors Smorstok** and **Maus** at the Monticello Clinic . . . **Dr. Charles F. Schafer** has joined the Winona Clinic staff . . . **Dr. James Lueders** is practicing in Evansville . . . **Dr. Timothy Nealy** is Blooming Prairie's new physician . . . **Dr. John D. Nehring** has joined the Community Clinic in Wabasha . . . **Dr. Emil W. Johnson** is practicing in Echo . . . **Dr. Glenn Schroeder** has returned to Red Wing to set up an independent medical practice . . . **Dr. David K. McAfee** has joined the staff of the Lakeland Medical Center in Willmar.

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INTERNIST for 20-physician-clinic in prosperous Minnesota city. Salary negotiable first year, then full partnership. East Range Clinic, Virginia, Minnesota.

PART TIME INTERNIST OR GENERAL PRACTITIONER. Good compensation — Midway Area. Alfred F. Anderegg, M.D.; 2500 Como Avenue, St. Paul, Minnesota.

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WANTED — Internist, board certified or qualified, to associate with two board certified internists. Ten man multi-specialty group. (Lenont Peterson Clinic, Virginia, Minnesota) — Heart of the expanding taconite industry.

WANTED: young general practitioner to join six-man group consisting of 4 GPs, a general surgeon, and radiologist. College town of 22,000, 30 miles from Twin Cities. Also need LOCUM TENENS in general practice. Contact: Ed Jenkins, Mgr., River Falls Medical Clinic, River Falls, Wisc. Phone 425-5322.

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WANTED: Young internist and pediatrician, board certified or eligible, to join 6-man group consisting of 4 GP's, a general surgeon, and a radiologist. College town of 22,000 only 30 miles from Twin Cities. Salary open with early partnership opportunity. Write or call collect: Ed Jenkins, Mgr., River Falls Medical Clinic, River Falls, Wisc., phone 425-5322.

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WANTED: GP to join clinic serving population area of 12,000. City has new hospital, new clinic building, two nursing homes, new Jr-Sr high school, new swimming pool, rich farming area in Red River Valley. Fishing and hunting nearby; metropolitan city close by. Salary open and partnership if interested. Write or call Warren Clinic, Warren, Minnesota 56762. 742-6231, area code 218.

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WANTED—INTERNIST, Board certified or qualified to associate with 5-doctor clinic. In growing economy of industrial and Summer and Winter tourist area. Grand Rapids Clinic, Grand Rapids. Telephone 1-218-326-3436.

FOR RENT—Modern, air-conditioned building readily adaptable for a group of doctors or clinic located near 44th and France in highly desirable Edina-Morningside of Minneapolis. Adjacent parking. Contact owner, Ted Shirley, 926-3460.

DON'T OVERLOOK THIS . . . 3 months' rent free in modern medical clinic—successful location in N.W. suburb of Minneapolis. Come see anytime—36th and Noble Avenue North. Noble Drug, Ju 8-9449, Ben or Lou.

WANTED: OB-GYN in well established group in city of 15,000. Good hunting and fishing, we have over 1,000 lakes in county. Excellent hospital and clinic facilities. Write: V. I. Hanson, Business Manager, Park Region Medical Center, Fergus Falls, Minnesota.

FOR SALE: Prof X-ray machine (portable) price $200. My phone number is FE 8-0935, Minneapolis.

PSYCHIATRIC RESIDENCIES—positions available January and July 1967. Fully approved; balanced didactic and clinical program. Three programs from which to choose; three-year program, $8,352 to $9,500; five-year career program, $9,500-$17,184: N.I.M.H. General Practitioner stipends, $12,000. Located in Michigan's Water Winter Wonderland. Contact Dr. Paul Kauffman, Director of Training, Traverse City State Hospital, Traverse City, Michigan. An equal opportunity employer.

WANTED: a general practitioner—present physician retiring after fifty years. Good community, churches, school, stores and bank. New Hospital. Write: MINNESOTA MEDICINE-360, 496 Lowry Medical Arts Building, St. Paul.

G. P., age 31, two years experience, married with family, would like to relocate, limiting practice to medicine and pediatrics. Write: MINNESOTA MEDICINE — 361; 496 Lowry Medical Arts Bldg., St. Paul 55102.

PHARMACIST with five years' laboratory experience would like to contract pharmacy and laboratory in two or more doctor clinic. Write: Eugene Ommen, 1930 Howard Avenue, Waterloo, Iowa.

AVAILABLE SOON: Fascinating General Practice Partnership for sale in pleasant central California community just two hours from the ocean on high Sierras. Gross over $160,000 although each partner off 30% of the time in the past six years. Excellent duck, pheasant and deer hunting nearby. Profitable hospital laobratory and X-ray service included. Office conveniently located in hospital with open staff. Homes available if desired. Also, lake and ski cabin in North Shore Lake Tahoe Area. Terms negotiable near fair value. Write: MINNESOTA MEDICINE — 362; 496 Lowry Medical Arts Building, St. Paul 55102.

Ugliness

It was not until I had attended a few post-mortems that I realized that even the ugliest human exteriors may contain the most beautiful viscera, and was able to console myself for the facial drabness of my neighbors in omnibuses by dissecting them in my imagination. — J. B. S. Haldane

Virtue

Be not simply good; be good for something. — Thoreau

Medical Economics

Gifts Offer Tax Savings

We have discussed tax saving opportunities through the use of trusts, wills and marital deductions. Another avenue for estate tax and income tax savings is through the use of gifts. Present regulations permit an individual to make tax-free gifts of $30,000 *to all donees* during his lifetime without incurring gift tax liability. This is known as the "Specific Exemption." An individual may also make gifts of up to $3,000 per year *to each* donee without incurring liability. Regulations provide further that a gift made by a husband or wife may be treated, for gift tax purposes, as though made one-half by each. This provision has the effect of increasing the annual exemption to $6,000 and the "Specific Exemption" to $60,000 without gift tax liability. In order to qualify for the "Joint" treatment of gifts, both must be citizens or residents of the United States, the person making the gift must not give his wife or husband power of appointment over the gifted property, neither can they remarry during the calendar year of the gift and both must give their consent to so treating the gift.

Gifts to a spouse are also accorded special treatment. The exemption allowed is one-half the value of the property given. This exclusion is in addition to the $30,000 specific and $3,000 annual exemptions.

To illustrate the estate tax savings opportunities, assume a gross estate of $300,000, a wife and no children. The estate is to go first to the wife and upon her death to charities. If you hold all this property in your estate, the taxable estate will be $90,000 ($300,000-$150,000-$60,000) and Federal Estate Tax will be about $17,500. If, on the other hand, you give $100,000 to your wife, the estate tax will be only $4,800, an estate tax saving of $12,700. In order to qualify, these gifts must be made three years or more prior to death to avoid being held as made in contemplation of death and thrown back into the gross estate.

In this example, the transfer would require seven calendar years to avoid gift tax liability, $66,000 could be given during the first year using $33,000 marital gift deduction, $30,000 lifetime deduction and the $3,000 annual deduction. This would leave $34,000 to be gifted out during the next six years at $6,000 per year.

Using the same example, assume you have three children and intend your property to go to your wife and children. Without gift or trust provisions, the estate tax would again be $17,500, but by making gifts in trust or outright to your children of $100,000, the tax would reduce to $4,800. Such transfer would take three calendar years with $78,000 going out the first year, $18,000 the second and $4,000 the third year. To illustrate the income tax savings, assume you are in a 50% tax bracket and the $100,000 is earning $6,000 per year in dividends. You would pay $3,000 income tax on these dividends but the children will only pay approximately $700, an annual tax savings of $2,300.

The basis of property *for gift tax purposes* is its fair market value on the date of the gift. The basis of the gift *for gain purposes* is the same as the basis in the hands of the last donor who received it other than by gift. This points up an important and often neglected factor — that of keeping complete and adequate records to clearly reflect these bases. Whether you are the recipient of a gift or the donor, it is very important that you secure the data and keep a permanent record of such information for gift tax and income tax purposes.

The field of gifts is so very closely related with the use of trusts and estate planning and a decision regarding a gift must be considered from all angles. For this reason, it is important to make these decisions only upon the advice of your attorney after properly weighing all factors. Gift provisions, if used judiciously, can provide a useful avenue for tax-free transfer of sizeable amounts of property over a period of years.

William D. Huntington*
Minneapolis, Minnesota

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*Northern Division Manager, Professional Management Midwest.

When you shut your eye to temptation, be sure you don't make it look like a wink. — Richard Armknecht

Sustained circulatory, respirator
and cerebral stimulation for th

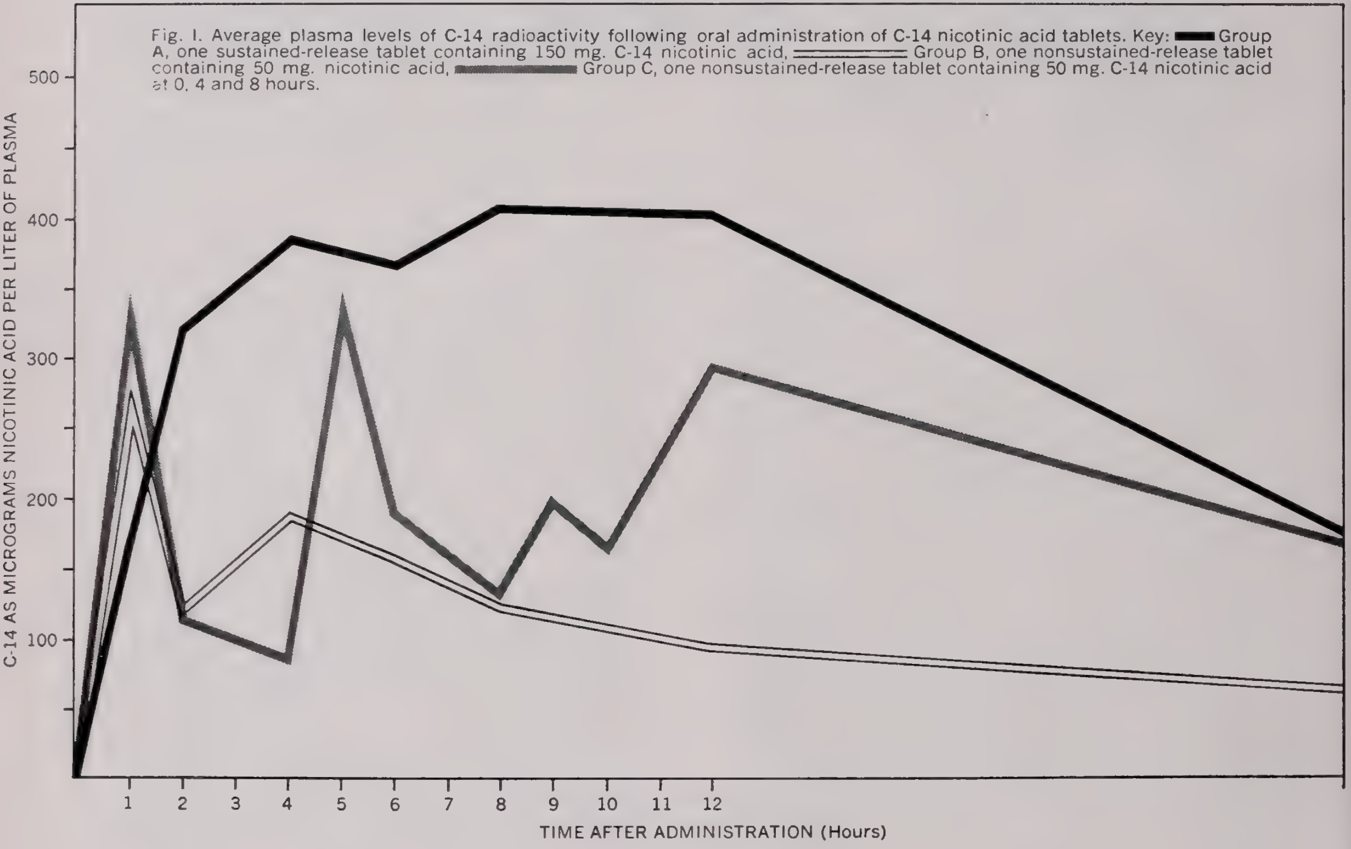

Fig. I. Average plasma levels of C-14 radioactivity following oral administration of C-14 nicotinic acid tablets. Key: ━━ Group A, one sustained-release tablet containing 150 mg. C-14 nicotinic acid, ═══ Group B, one nonsustained-release tablet containing 50 mg. nicotinic acid, ▬▬ Group C, one nonsustained-release tablet containing 50 mg. C-14 nicotinic acid at 0, 4 and 8 hours.

(fewer absent doses by absent-minded patients)

Human volunteer subjects were administered Geroniazol TT tablets with the nicotinic acid component made radioactive with C-14. Plasma and urine samples were analyzed. (See Figures I and II) The radioactive tracer study substantiated the previous clinical evidence that the release of nicotinic acid from the Geroniazol TT tablet produced a gradual rise in plasma levels to a plateau for a total of 12 hours and more.

Such proven sustained activity makes the management of geriatric patients much easier by minimizing the possibility of neglected doses through absent-mindedness or senile confusion. Therapy *can* be continuous on a daily dose of only one Geroniazol TT tablet every 12 hours.

The gradual release of nicotinic acid in Geroniazol TT will provide the well-known peripheral vasodilatation needed in patients with deficient circulation and with a minimum amount (if any) of "flushing." Also, cerebrovascular circulation is complemented by pentylenetetrazol, long-established as a cerebral and respiratory stimulant.

Geroniazol TT improves the typical, unfortunate, signs of senile confusion. Patients become more alert,

ged and debilitated

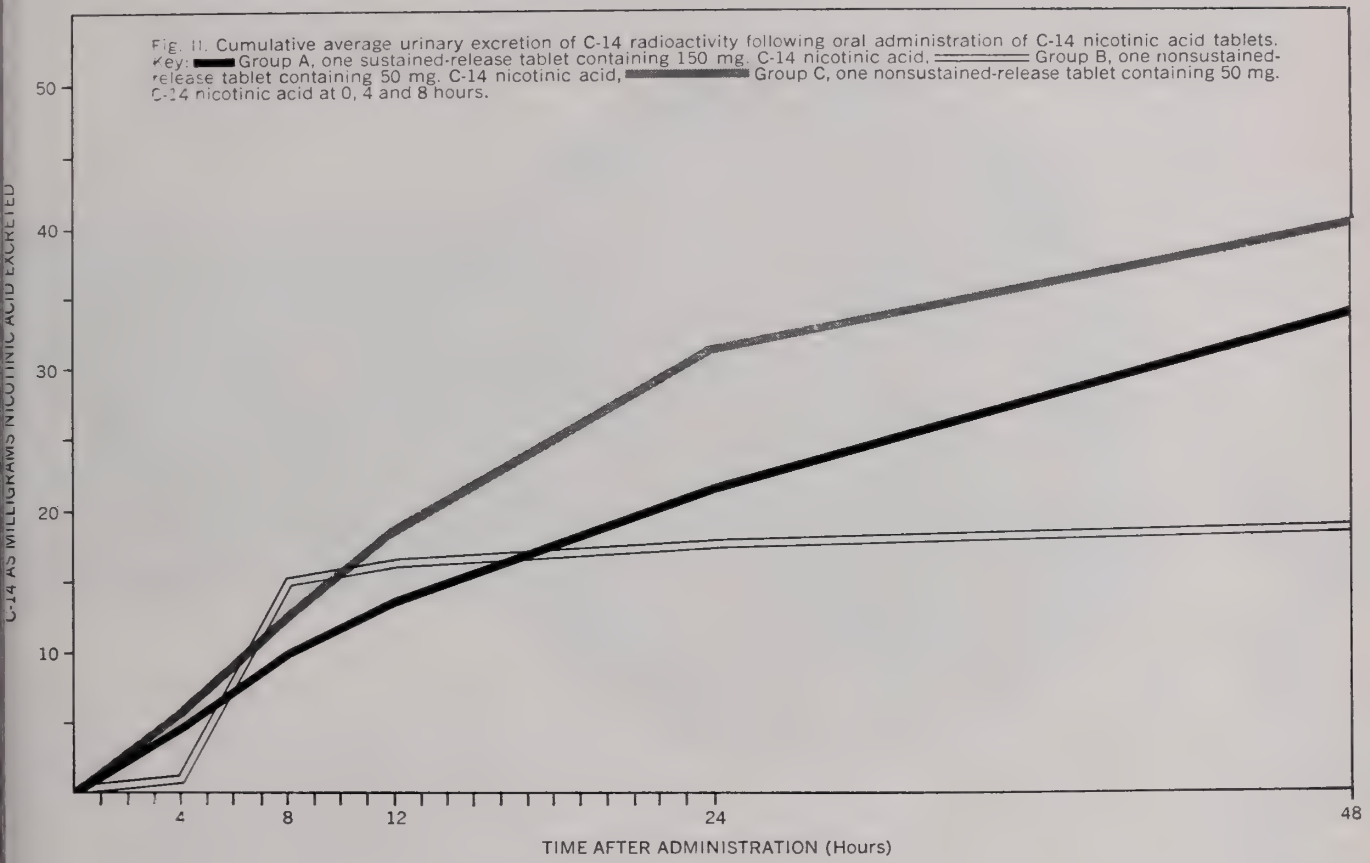

Fig. II. Cumulative average urinary excretion of C-14 radioactivity following oral administration of C-14 nicotinic acid tablets. Key: ▬ Group A, one sustained-release tablet containing 150 mg. C-14 nicotinic acid, ═ Group B, one nonsustained-release tablet containing 50 mg. C-14 nicotinic acid, ▬ Group C, one nonsustained-release tablet containing 50 mg. C-14 nicotinic acid at 0, 4 and 8 hours.

less confused and moody. Personal care, memory, emotional stability, social attention improve. Fatigue, apathy and irritability are reduced.

A prescription for 100 tablets of Geroniazol TT will permit your patients to enjoy the benefits of time-prolonged nicotinic acid/pentylenetetrazol therapy, at an economical price. Dosage is only one tablet every 12 hours.

Contraindications: There are no known contraindications.

Precautions: Exercise caution when treating patients with a low convulsive threshold.

Side Effects: Side effects are rarely encountered, however due to the vasodilatation effect of nicotinic acid, transitory mild nausea, flushing, tingling and pruritus are possible.

Dosage: One tablet every 12 hours.

Supplied: Prescribe bottles of 100 tablets, to take advantage of recent price reduction.

References: 1. Report by Nuclear Science & Engineering Corp., Pittsburgh, Pa., in files of Philips Roxane Laboratories. 2. Connolly, R.: W. Virginia Med. J. *56*:263 (Aug.) 1960. 3. Curran, T. R., and Phelps, D. K.: Am. Pract. & Digest Treat. *11*:617 (July) 1960.

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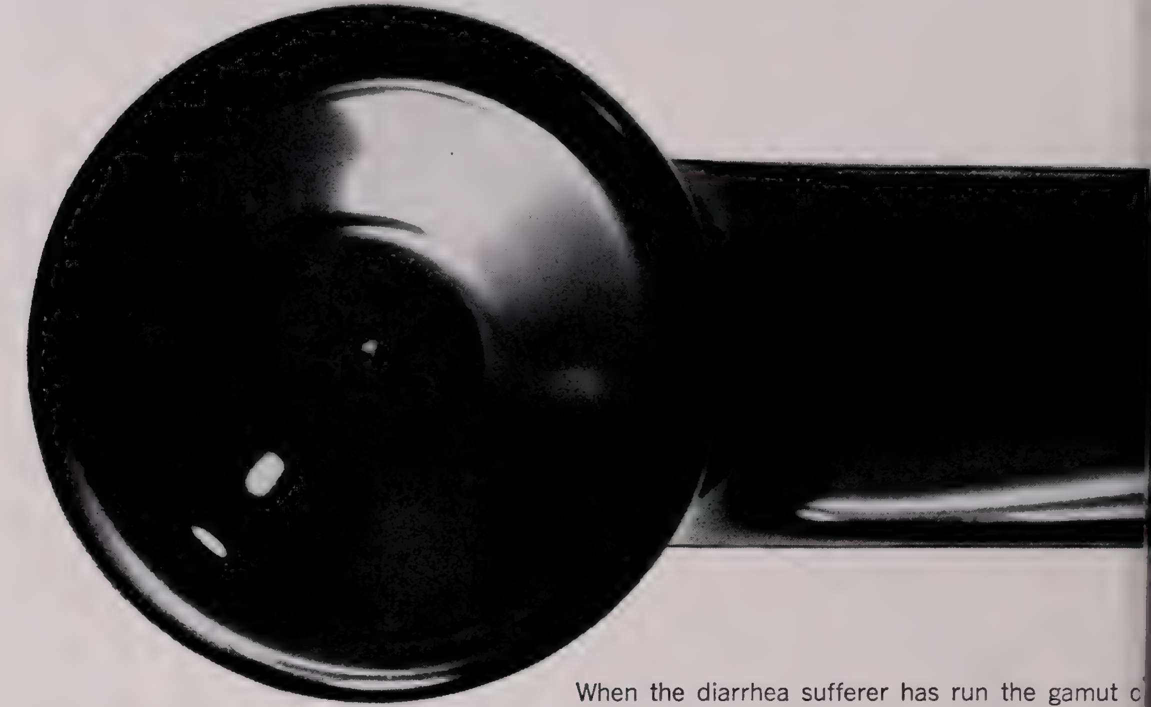

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CONTRAINDICATIONS: Do not use in intestinal obstruction, e
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to sulfonamides or neomycin; in pregnancy at term, in prematu
infants, or during first week of life in the newborn.

WARNINGS: Use only after critical appraisal in patients wi
hepatic or renal damage, urinary obstruction, or blood dyscr
sias. Fatal hypersensitivity reactions and blood dyscrasias r
ported with use of sulfonamides. Consider periodic blood count
hepatic and renal function tests during intermittent or chron
use.

PRECAUTIONS: Succinylsulfathiazole: Use with caution if the
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requires supplementary vitamins B_1 and K. *Neomycin:* Watch f

your ℞ for
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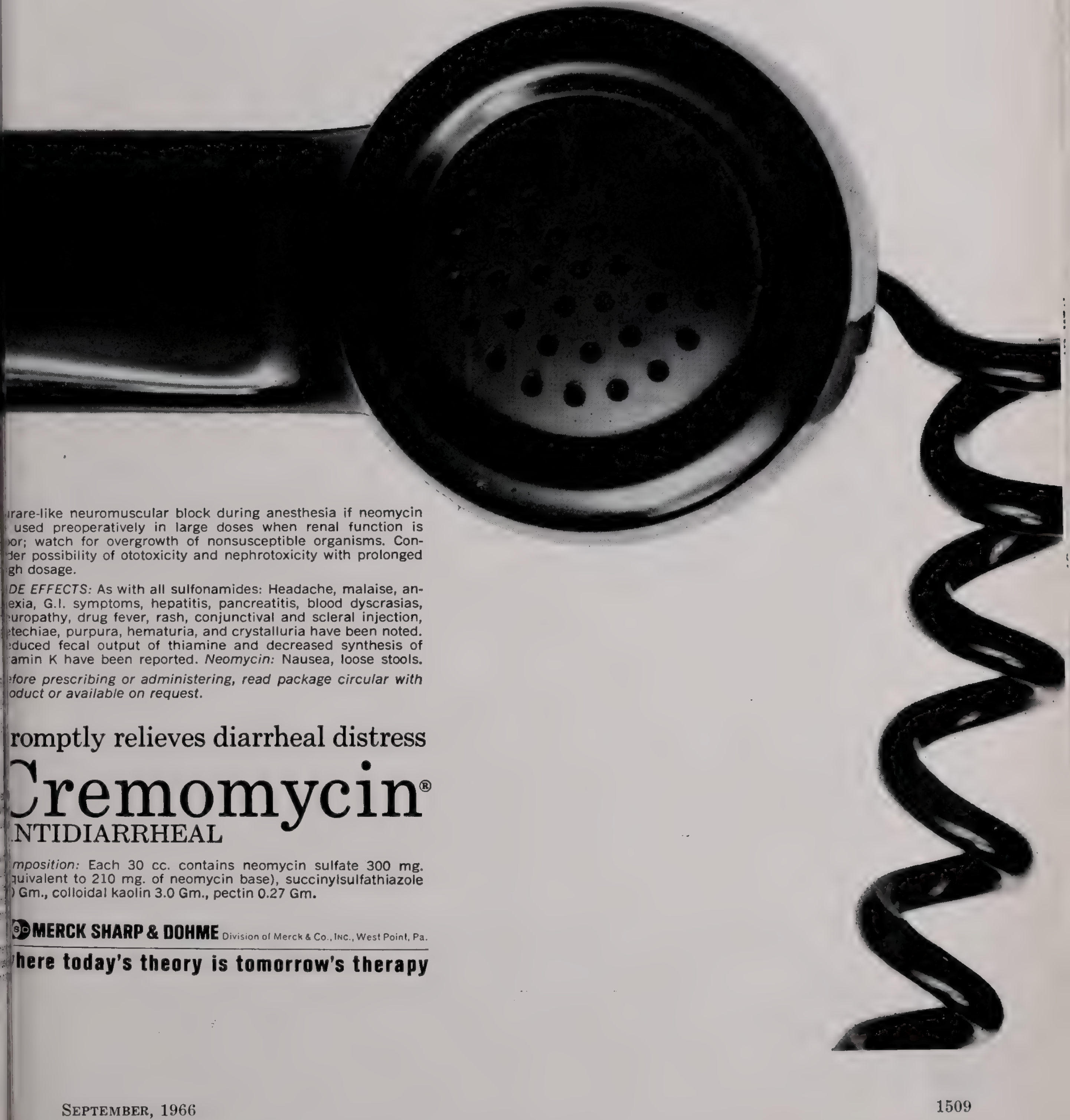
can provide relief



rare-like neuromuscular block during anesthesia if neomycin used preoperatively in large doses when renal function is or; watch for overgrowth of nonsusceptible organisms. Conder possibility of ototoxicity and nephrotoxicity with prolonged gh dosage.

DE EFFECTS: As with all sulfonamides: Headache, malaise, anexia, G.I. symptoms, hepatitis, pancreatitis, blood dyscrasias, uropathy, drug fever, rash, conjunctival and scleral injection, techiae, purpura, hematuria, and crystalluria have been noted. duced fecal output of thiamine and decreased synthesis of amin K have been reported. *Neomycin:* Nausea, loose stools.

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Minnesota Medicine at a Glance

Anovulatory Syndrome — Spellacy and Cohen Page 1357

The successful treatment of the anovulatory syndrome in one instance does not constitute an assurance of the effectiveness of a drug, but since other methods of treatment are on the whole unsatisfactory, the use of Clomiphene may be worth a trial.

Large Bowel Obstruction — DeShazo et al. Page 1361

Because of the presence of air in the large bowel, as well as in the small gut, the differentiation of a large bowel obstruction from paralytic ileus may on occasions be difficult. By the process of doing a barium enema and a sigmoidoscopic examination in order to remove the distally situated gas, a differentiation can often be made. It is, therefore, well to keep this in mind in order that proper therapy can be instituted without undue delay.

Gangrene of the Foot — Loeb and Sako Page 1365

Acceleration of gangrenous changes of ischemic extremities is one of the unfavorable complications following sympathectomy. An interesting case of this paradoxical* response following lumbar sympathectomy is reported. Very careful preoperative and intraoperative studies were performed. These would indicate that the patient should expect a favorable response to sympathectomy. A possible etiologic mechanism for the unfavorable response obtained in this case is discussed.

Mitral Stenosis — Karnegis and Wang Page 1369

Mitral stenosis produces characteristic symptoms, signs, X-ray changes, electrocardiographic and phonocardiographic findings described in this paper. The formula for calculating mitral valve area from catheterization data is clearly explained. The authors present the need for accurate diagnosis and assessment of severity. They describe the Graham-Steell murmur implying relative pulmonary insufficiency. (However, when this murmur is found, usually aortic insufficiency is the cause. Ed.)

Iatrogenic Arterial Injuries — Bergan Page 1375

Galen, in the first century A.D., made reference to physician-induced arterial injury associated with blood letting. Even today inadvertent arterial injuries and complications of procedures, performed after standard methods, are noted to produce arterial injury. The author classifies and illustrates various types of arterial injuries with the use of several case reports. Awareness of the possibility of arterial injury and appreciation of the prompt treatment necessary are emphasized in this communication.

Urine Cultures in Women — Breitenbucher Page 1381

This study represents a very careful appraisal of voided "clean catch" urine cultures in women. Ninety-nine percent of the women without clinical urinary tract infections had bacterial colony counts of less than 10,000 per cc. Of those women with clinical urinary tract infections, bacterial colony counts were greater than 10,000 per cc. in 98 percent.

---

*See Test Your Word Score, Page 1411.

Ninety-three percent had more than 50,000 and 74 percent more than 100,000 bacterial colonies per cc. of urine. The author concludes that "clean catch" voided urine specimens may be reliably used for culture in women.

Regional Enteritis — Mintz Page 1437

Regional enteritis is a granulomatous disease and may occur in any portion of the gastrointestinal tract. It is most commonly observed under the age of 40. It has four major classifications which may overlap: it may develop as an acute regional ileitis; ileo-jejunitis; it may affect the colon; it may be a chronic terminal ileitis.

Regional enteritis is associated with abdominal pain, diarrhea, weight loss, fever, and occasionally an abdominal mass; and there may be anemia. Three types of fistulae may occur: internal 41%, external 22%, and perirectal 38%. Among the uncommon signs and symptoms are arthritis, ocular difficulties, erythema nodosum, and splenomegaly. The disease can be confused with tuberculosis, chronic mesenteric arterial insufficiency, carcinoid tumors of the ileum, or the irritable bowel syndrome. The diagnosis can usually be confirmed by the roentgenologic findings.

Since the treatment for this disease is not specific there are a variety of treatments designed to control the disease or its complications, and though the mortality of this disease is not relatively high, the morbidity continues to remain alarming.

Cardiac Program for Physicians

The Ramsey County Heart Division of the Minnesota Heart Association, in cooperation with the United States Department of Health, Education and Welfare, is sponsoring an on-going series of cardiac conference programs.

The programs are being held at Charles T. Miller Hospital, 125 West College Avenue, St. Paul, and is open to all physicians free of charge.

This clinical conference brings together the departments of medicine, surgery, radiology, anesthesiology, and pathology in considering interesting aspects of cardiac disease.

The conference meets every other Wednesday, alternating with the established Cardiac Pathology conference.

A complimentary buffet luncheon is served at 11:45 a.m. in College Hall at the Charles T. Miller Hospital, and the lectures and conferences are held from 12:30 p.m. to 1:30 p.m., in the College Hall amphitheater.

For more information call the Minnesota Heart Association, 646-6554. Advance reservations are unnecessary.

It is only by medicine that one can arrive at some knowledge of human nature, — but on one condition, to embrace it in its true generality. — Hippocrates

---

If the workingman gets his hours reduced much more he will be in danger of meeting himself coming home every time he goes to work. — Frost

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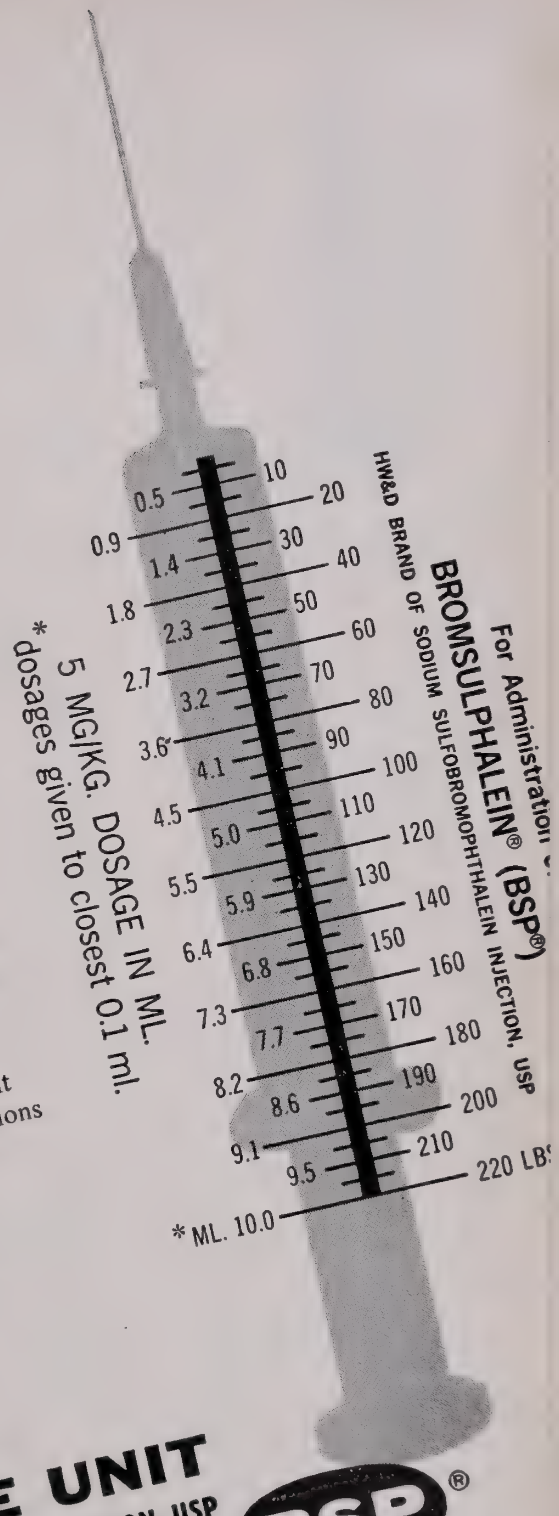
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Volume 49

Number 10

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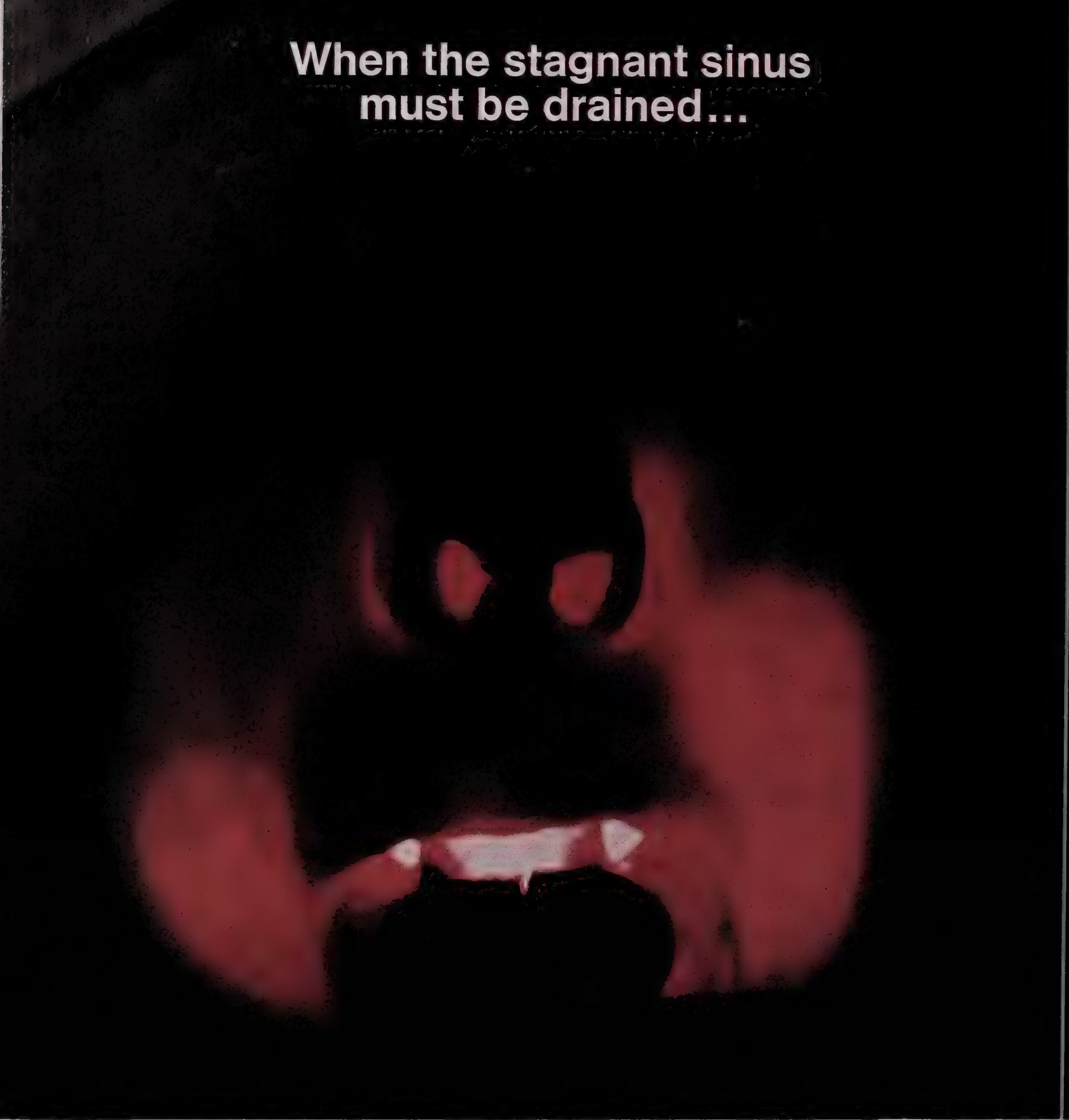

Transillumination of the sinuses—diffuse shadow on right side of face indicates unilateral maxillary sinusitis.

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President's Letter

At a recent meeting of the Organization of State Medical Association Presidents, a group which includes presidents elect and immediate past presidents as well, the multiple problems involving state associations uniquely different from the over-all involvement of the American Medical Association were the basis of the two-day session.

Ohio's problem with the Statement of Compliance, New York's experience with the implementation of Title XIX, multiple state concern with the problems of the in-hospital specialist were among the topics of the meeting.

Representatives of the Department of Health Education and Welfare appearing before the group reviewed current government regulations, discussed areas of apparent misunderstanding and explored probable areas of expanding Federal involvement in the practice of medicine and the development of medical man power.

Most of the problems reported by various States were common to all states, and while the Organization has no structure or authority to develop corrective measures as an organization, the exchange of ideas and suggestions and the full reporting of intrastate action where action was required constituted valuable experience for every state officer in attendance.

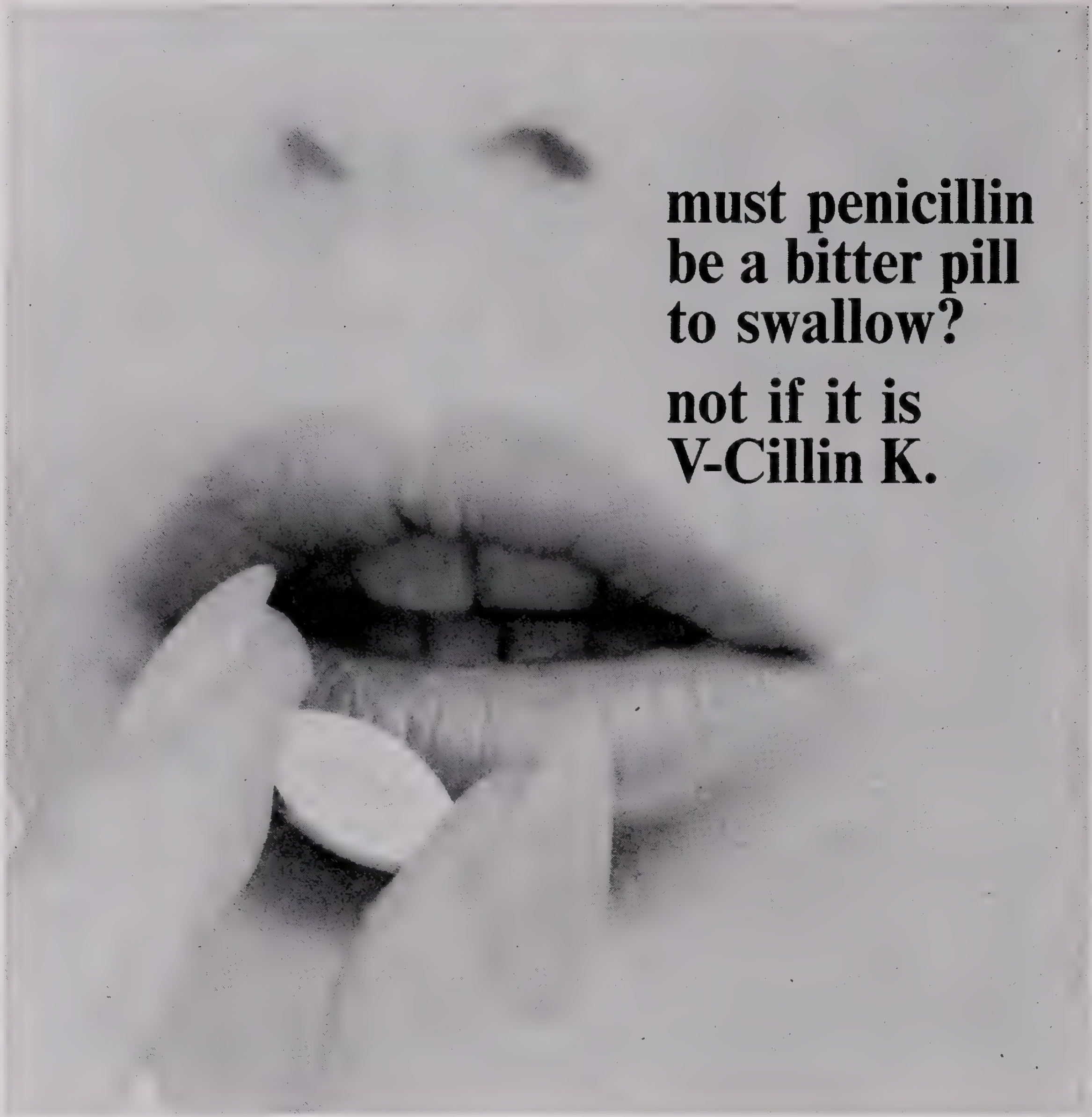
We physicians in Minnesota, however, have a different problem. Our problem has no governmental overtones, no patient-physician relationship, no assignments to sign or not to sign, a problem where participation is not debatable but is a must. This problem is the handicap under which our Association office operates. When the volume of work is weighed against the deficiencies of the office space in which it is produced, the number of workers who produce it and the continuing high quality of the result, those results seem incredible. Only dedication can explain the efficiency with which rapidly increasing demands are being met. Since there is no foreseeable end to these increasing demands, but since human dedication has an ultimate limit, our problem becomes obvious.

A committee Council appointed has been considering new physical arrangements ranging from renting to building. The House of Delegates, in approving a dues raise, considered and approved the need for increased sums to be spent on personnel additions. Combining these two actions, expediting a committee decision, proposing the project with a sound financial base to the Association as a whole must be a high priority Association activity.

Our other problems are many, but this present need, when met, will provide the mechanisms needed for a wider physician understanding of the problems, better physician-association rapport and better lives for our overburdened, highly efficient and loyal staff.

RP Buckley M.D.

R. P. Buckley, M.D.
President
Minnesota State Medical Association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The Case for Body Surface Area

As A Gauge for Drug Dosage

W. D. SNIVELY, JR., M.D.*
Evansville, Indiana

"Dosage is the heart of drug therapy. It is therapy in action. Right or wrong, it is the final expression of diagnostic and therapeutic acumen." *Harry C. Shirkey, M.D.*

SHIRKEY'S EMPHASIS on the importance of proper drug dosage is most timely. Modern drugs are among the physician's most powerful weapons against disease. Properly aimed, they are strikingly effective. Improperly aimed, they fail to hit the target, accomplishing nothing; worse, they may do harm.

Drug dosage deserves particular attention in pediatrics, because many childhood diseases are so acute, because children vary greatly in their susceptibility to potent agents, and because most pediatric doses represent casually or inaccurately derived fractions of adult doses.

Age as a Gauge

Not only is age of little worth as a gauge for dosage; it presents real hazards since it may yield an inadequate dose at a time of critical need or an overdose that may poison. Its unreliability stems chiefly from the great normal variations in size within a given age group. For example, a six-month-old infant girl may weigh from 12.7 to 20 pounds and still be normal. At 12 years of age the normal maximal weight is double the normal minimal weight. Such variations make age a highly unreliable criterion for dosage.

To compound the inaccuracy, ages are often bracketed arbitrarily for dosage purposes. For example, the ages from two to six years may be placed in one group; the ages six to 12 years in another group. A six-year-old could fall into either group. The two-year-old will probably get an overdose, the twelve-year-old an underdose. Shirkey[25] found that the maximal dose based upon such a vague recommendation could be 666% of the minimal dose. He therefore concluded, "Only honey or non-medicated syrups should be dosed according to age."

---

*Mead Johnson & Company, Evansville, Ind.; Clinical Professor, Department of Pediatrics, Medical College of Alabama.

Reprint requests to Dr. W. D. Snively, Jr., 2404 Pennsylvania St., Evansville, Ind. 47721

Weight as a Gauge

While weight surpasses age as a gauge for pediatric drug dosage when applied to infants and children of about the same age, it is not reliable when applied to patients of different ages since the dose of most drugs is not a simple linear function of body weight. Hence, dosing on the basis of so much per kilogram body weight can cause gross inaccuracy. Using weight as the gauge, the correct dose for an infant or small child will usually be excessive when applied to a larger child or to an adult. For example, the recommended daily dose of sulfadiazine for the older infant is 150 mg./kg. If this is used as a basis for calculating the dose for an adult, it results in the administration of 10.5 Gm./day instead of 6 Gm./day, the recommended dose for an adult.

Valiant attempts have been made to correct for the unreliability of dosage based on weight. They have resulted in arbitrarily chosen categories with a different per-weight unit for each category. As will be shown below, such dosage schedules overtax the memory. They force physicians to rely on schedules printed on blotters, cards, calendars, and other give-aways. They shackle the physician to memory aids except in the case of simple drugs that he uses frequently.

Body Surface Area as a Gauge

A rich body of scientific evidence has demonstrated a rough quantitative relationship between body surface area and such fundamental physiologic measurements and processes as heat production, cardiac output, plasma volume, glomerular filtration, blood pressure, organ size, oxygen consumption and nitrogen requirement.[2,3,4,5,6,7,8,9,10,13,14,18,21] On the basis of this relationship, one can reasonably suppose that the magnitude of the individual's physiologic struggle to maintain life can be measured by the area of his exposure to the external environment. The several systems of the body support the individual in that struggle. The area of the body surface, therefore, provides a useful index of the activities of the body systems. As an example, requirements for water and electrolytes have been shown to be roughly proportional to body surface area.[12,15,22,23] So have the optimal doses of drugs in therapy.[16,24,25,27,28]

We can well ask: "Why is body surface area the best measurement on which to base dosage?" The reason relates to our ancestral Protozoan, whose cell membrane was a versatile, all-important structure directly concerned with the functions of nutrition, circulation, excretion, respiration, and locomotion. With the coming of multicell organisms, functions became localized and special structures were evolved to perform them. For example, the digestive tract began as an external surface lined with endodermal cells. Then invagination occurred. The end result was an elongated digestive tube closed except for openings at the head and tail of the organism. Other functions were taken over by appropriately specialized organs.[23]

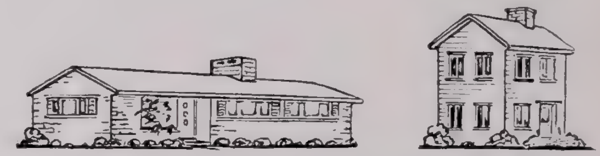

Fig. 1 — The elongated ranch house has more surface area in relation to volume than does the two story conventional house.

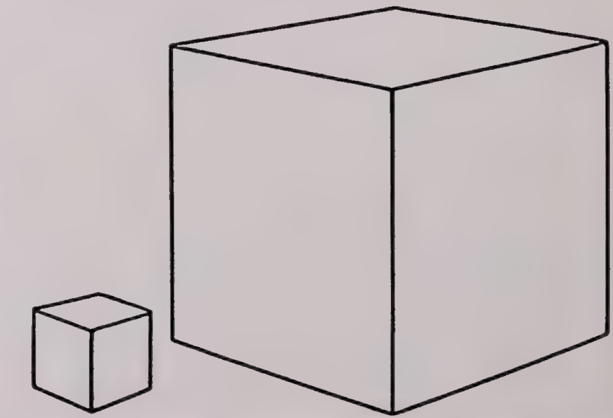

Fig. 2 — Ratio of surface area to volume of the small (2 in.) cube is 3:1. Ratio of surface area to volume of the large (8 in.) cube is .75:1.

Yet with all the progress made by mammals toward complexity and specialization of function, the mammalian body surface still corresponds anatomically to the cell membrane of the Protozoan. Because of this correspondence, body surface area provides a quantitative, though approximate, index of our total metabolic activity. Thereby it provides us with a remarkably useful gauge for dosage.

In 1950 Crawford and others[16] described how the surface area principle could simplify dosage. They used body surface area as the common denominator in the calculation of doses of a large variety of drugs for more than a year for patients ranging from small prematures to young adults. Their clinical results suggested that body surface area offers greater simplicity and accuracy than do calculations based on age or weight. Since their paper appeared, body surface area has been taught as a gauge for dosage in more and more medical schools. Leading textbooks in the field of pediatrics present drug doses in terms of surface area as well as in terms of weight.[24,27] The current dose recommendations from the Children's Service, Massachusetts General Hospital, gives drug doses chiefly in terms of surface area.[29] Surface area as a gauge for dosage has the authoritative support of the Council on Drugs of the American Medical Association.[28] Subscribers to the National Formulary XII, published in September, 1965, received a handbook on Drug Dosage[26] with each copy of the Formulary. The handbook gives doses in terms of surface area, thus making available the surface area method to every pharmacy school, most pharmacy graduates, and countless laboratories and libraries.

Relation of Surface Area to Weight, Volume, and Configuration

The shape and dimensions of an object determine the ratio of its surface area to its weight or volume. An elongated object has more surface area in relation to volume than does a squarish object of equal volume. Thus, a single story, modern ranch house with dimensions 50 × 25 × 10 ft. has a volume of 12,500 cu. ft. Its surface area is 4,000 sq. ft. An old-fashioned conventional style house with dimensions of 25 × 25 × 20 ft. has a volume of 12,500 cu. ft. and a surface area of only 3,250 sq. ft. Because of its smaller surface area such a house would be more appropriate for cold climates because it would be easier to heat. See Figure 1.

A small object has a relatively larger surface area than does a larger object. Thus, a 2-inch cube has a volume of 8 cu. in. and a surface area of 24 sq. in. The ratio of

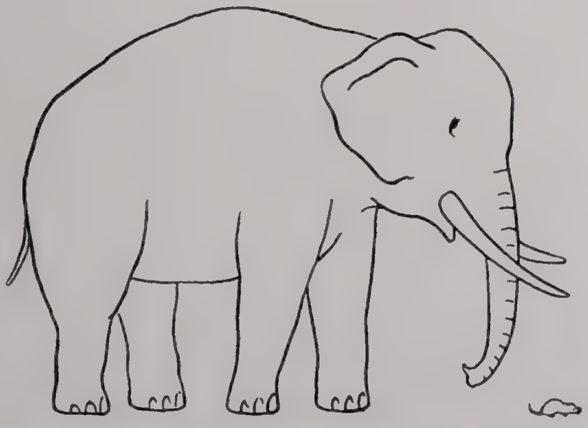

Fig. 3 — The shrew has approximately 42 times as much surface area in relation to weight as does the elephant.

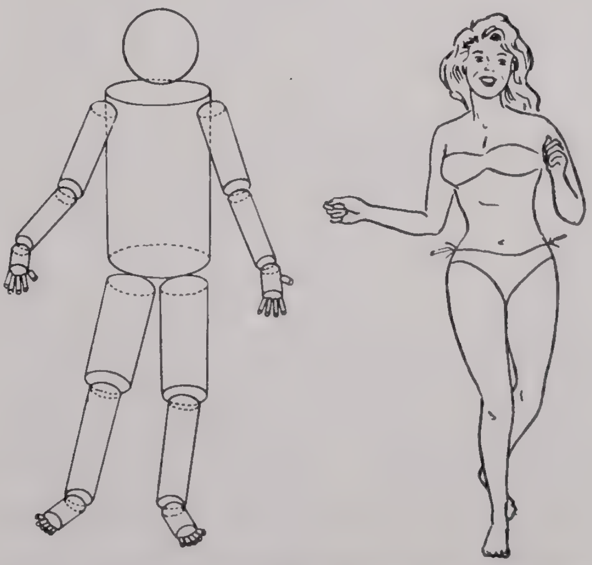

Fig. 4 — Mathematically the human body resembles a series of cylinders topped by a sphere.

surface area to volume is 3:1. An 8-inch cube has a volume of 512 cu. in. and a surface area of 384 sq. in. The ratio of surface area to volume is .75:1. See Figure 2.

The mathematical explanation for these relationships is that surface area increases or decreases as the square of linear dimensions while weight or volume increases or decreases as the cube of linear dimensions.

A small object has a greater surface area in relation to its weight or volume than does a large object. Thus a shrew weighing 60 Gm. has 42 times as much surface area in relation to weight as does an elephant weighing 5,500,000 Gm. See Figure 3.

Similar relations apply to round or curved objects such as the human body, which, reduced to its geometric elements, resembles a series of cylinders topped by a sphere (admittedly an inappropriate description for a pretty girl). See Figure 4.

How to Determine Body Surface Area

Undoubtedly the difficulty involved in measurement of body surface area explains why it has not been more generally used. Methods used by investigators have involved simple covering, geometrical measurement, measurement of the skinned hide, photographing the silhouette, measurement of electrical currents, and so forth. Such methods are obviously impractical for everyday use. Hence, formulas based upon height and weight were devised for estimating the approximate body surface. These formulas were incorporated into nomograms* including those of DuBois[2,11,17,19] and somewhat refined nomograms developed by Sendroy.[20] Obviously, one must know the height and weight of the patient and in addition have a nomogram available if this method is to be used. But heights and weights are not always known or are not always procurable and nomograms can be lost. The West table, which permits one to determine body surface area on the basis of weight alone, has been recommended by Shirkey and Barba.[24] It is most reliable when used for children of approximately normal body configuration. The author and his colleagues[30] estimated the surface areas of 266 children by use of the West table and the Sendroy nomogram. Statistical comparison of the results of the two methods showed a standard deviation of 11.45%, satisfactory for clinical purposes. They developed an alternative method requiring nothing but a tape measure. It utilizes the sitting height (crown-rump length) method through use of a formula. For children *six months and under* one uses the formula:

$$\text{Surface area} = 0.00017\ (\text{sitting height in cm.})^2 {}^{**}$$

For children *over six months* one uses the formula:

$$\text{Surface area} = 0.00019\ (\text{sitting height in cm.})^2$$

Results derived by the sitting height formula were compared statistically with those found by use of the Sendroy nomogram. The standard deviation for children six months and under was 6.66%; for children over six months the standard deviation was 7.55%.

The rationale for the sitting height formula rests on the accepted theory of the origin of man and provides evidence supporting that theory. Examination of the formula reveals that surface area is proportional to the square of the sitting height. Why should this be? Man's ancient aquatic ancestor was a worm-like creature not too unlike Amphioxus. It had a straight gut running the length of its body. The length of the gut was, of necessity, proportional to the length of the body. As evolution occurred over countless millenia, multiples of this proportion were maintained, even though the gut became convoluted and elongated to the point that it was many times the length of the body.

Today, for a given species, the length of the gut is still proportional to the length of the body. Now the measurement of man that corresponds to the body of his ancient ancestor is not his *total length* or *height* but his *crown-rump length* or *sitting height*. Arms and legs, it must be recalled, are phylogenetically not part of body length, but are lateral extensions of the body, originating in the fins of the Crossopterygian, the first fish to come ashore.

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*See Test Your Word Score, Page 1573.

**The expression (sitting height in cm.)^2 means the square of the sitting height measured in centimeters.

While the length of the gut is proportional to the sitting height, the area of the gut is proportional to the square of the sitting height. Von Pirquet explained why this is so.[1] He cited the work of Henning who found that the length of the intestinal canal on an average equals ten times the sitting height. "Direct measurements of the surface of the intestines gave for the undilated canal of an adult about 5000 sq. cm.; for the dilated, about 10,000 sq. cm.: if we take a medium of 7500 sq. cm., this corresponds to an average circumference of about one tenth of the sitting height. We can, therefore, have a conception of the absorbing surface in multiplying ten times the sitting height by one tenth of the sitting height, or, in other words, we take the square of the sitting height as a symbol of the absorbing surface."

Since the gut originated as an invagination or infolding of the body membrane of the Protozoan, I reasoned that the sitting height squared might well be proportional to body surface area. Simple arithmetic comparisons and, later, computer analyses, showed this to be the case.

While the simple West table for derivation of surface area by weight alone is widely useful and while it meets most needs for determination of surface area, the sitting height formula has the following possible uses:

1. It can be used as the chief method of determining body surface area when the weight is not known or not obtainable. It should thus prove useful in emergency situations and in developing countries.
2. It can be used when weight or a weight-surface nomogram or both are not available.
3. It can be used to check the value for surface area arrived at by other methods.

Limitations of Body Surface Area

While body surface area is undoubtedly the best single gauge for dosage, it should not be the sole gauge in dosing neonates and premature infants. For these no rule, however general, suffices. Doses must be individualized if they are to meet the needs of the infant for the situation in question. Indeed, use of body surface area for older infants and children really provides only an initial dose — and, of necessity, an *average* initial dose, that must be modified and adjusted later in accordance with the individual tolerance, requirement and clinical progress of the patient.

While body surface area appears to be the best gauge for dosage for adults as well

TABLE 1
Equivalent Sheet

Weight in Pounds	Sitting Height in Centimeters (crown-rump length)	Body Surface Area (square meters)	Single Dose of Liquid Pediatric Pharmaceuticals (in milliliters)
4.4	30	0.15	1.5
8.8	36	0.25	2.5
13.2	44	0.33	3.3
17.6	46	0.40	4.0
22.0	49	0.46	4.6
33.0	58	0.63	6.3
44.0	66	0.83	8.3
55.0	71	0.95	9.5
66.0	75	1.08	10.8
77.0	79	1.20	12.0
88.0	83	1.30	13.0
99.0	86	1.40	14.0
110.0	89	1.51	15.1
121.0	91	1.58	15.8

TABLE 2
Dose Instructions for REX®*
Give 4 times daily the dose corresponding to the figure closest to the child's weight or sitting height

Weight (in kg.)	Sitting Height (in cm.)	Body Surface Area (in M^2)	Dose of REX® (in ml.)
4	36	0.25	2.5
8	46	0.4	4.0
15	57	0.6	6.0
20	64	0.8	8.0
30	75	1.0	10.0
35	79	1.2	12.0
45	86	1.4	14.0
55	92	1.6	16.0

Calculations showing conversion of weight or sitting height to body surface area are not shown, but by using weight or sitting height to determine body surface area you can dose with great simplicity and accuracy.
For children with extremely unusual body configurations use a surface area nomogram or calculator, which utilizes height and weight to determine body surface area. Note that the basic dose for REX® is 10 ml. per M^2 body surface area four times daily.

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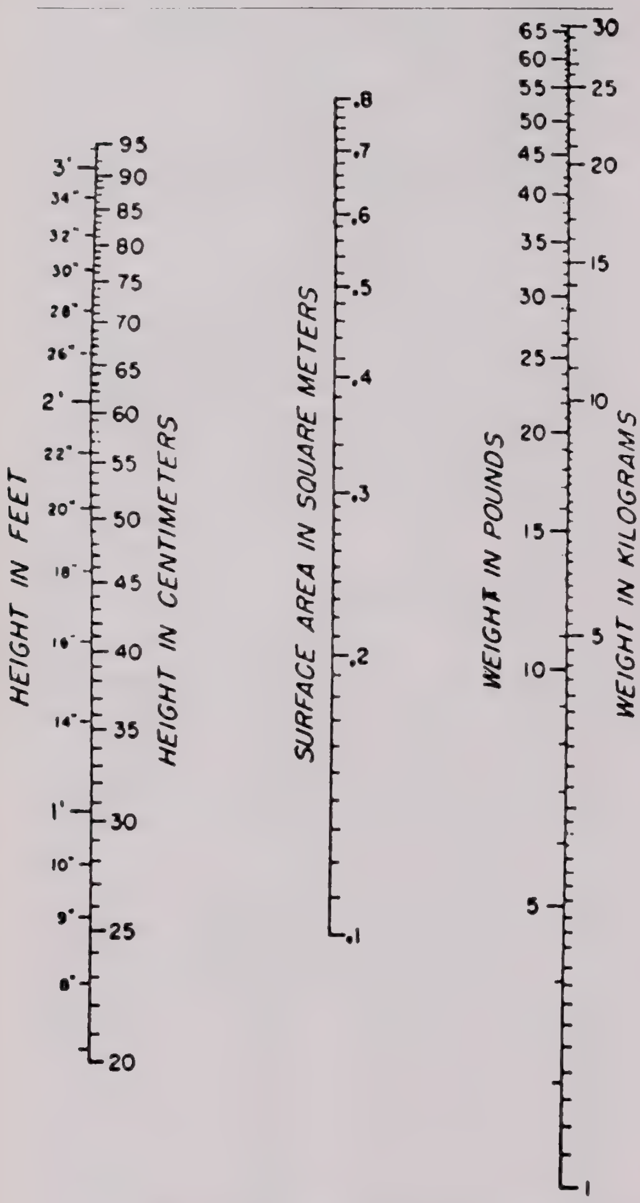
*REX® is an imaginary product.

as for children, we have tested the validity of the weight conversion nomogram (West table) and the sitting height formula statistically only in infants and children. Even in the case of infants and children, those with unusual body configuration might well have their surface area measured by use of the DuBois or Sendroy nomograms.

TABLE 3



Body Surface Area Nomogram for Infants and Young Children

To determine the surface area of the patient draw a straight line between the point representing his height on the left vertical scale to the point representing his weight on the right vertical scale. The point at which this line intersects the middle vertical scale represents the patient's surface area in square meters.

Used by permission of Talbot, N. B.; Sobel, E. H.; McArthur, J. W., and Crawford, J. D.: Functional Endocrinology From Birth Through Adolescence, Cambridge, Mass., The Commonwealth Fund, Harvard University Press, 1952.

Body Surface Area in the Dosing of Electrolytes

Body surface area as a gauge for dosage has, as noted above, enjoyed wide use in calculating doses for water and electrolytes. Its superiority over the use of body weight or age can be seen readily, since requirements for these substances when expressed in terms of body weight vary greatly from one age group to another. Thus the young infant has an average water intake of 70 ml./lb., while that of the ten-year-old is 35 ml./lb., and that of the adult, 25 ml./lb. Similarly, the infant has an average intake of 1.3 mEq. of sodium per pound compared to an average of 0.8 mEq. per pound for the ten-year-old and 0.5 mEq. per pound for the adult. But the average daily maintenance requirement for water is 1500 ml./M^2/24 hrs. regardless of age. The average daily maintenance requirement for either sodium or potassium is 50-70 mEq./M^2/24 hrs. These values apply to individuals of all ages. Even the maintenance requirement for carbohydrate can be expressed in terms of body surface: the average daily maintenance requirement is 60-75 Gm./M^2/day.

Iron, while not ordinarily considered an electrolyte, can also be dosed by use of body surface area. Consider the recommendations for dosage of a ferrous sulfate drop preparation, Fer-In-Sol^R, for prevention of iron deficiency when age groups are used as a dosage gauge:

Infants and young children	0.3 ml.	(Provides 7.5 mg. iron)
Older children	0.6 ml.	(Provides 15 mg. iron)

Such dosage can be simplified by using body surface area as the dosage gauge, in which case the dose becomes:

0.6 m./M^2/24 hrs. (Provides 15 mg. iron)

Consider the treatment of iron deficiency anemia when age is used as a gauge:

Infants	4-5 doses of 0.6 ml.	(Provides 60-75 mg. iron)
Children 2 to 6	5-7 doses of 0.6 ml.	(Provides 75-105 mg. iron)
Older children	7-10 doses of 0.6 ml.	(Provides 105-150 mg. iron)

How much simpler merely to use:

6 ml./M^2/24 hrs. (Provides 150 mg. iron)

Body Surface Area in the Dosing of Pediatric Pharmaceutical Products

We will confine our discussion of the use of body surface area as a gauge for dosage to pediatric pharmaceutical products, since it is for such products that surface area sees its greatest usefulness. Obviously, the more potent the drug to be used, the more critical is the dosage. Yet accuracy in dosage is desirable even for relatively innocuous drugs if one is to achieve the maximal results without side reactions.

The application of surface area can be demonstrated by examples. First, let us consider liquid products:

TEMPRA® Syrup and Drops

Using age as dosage gauge:

Age (Years)	*Doses 3-4 times daily* *Drops*	*Syrup*
Under 1	0.6 ml.	½ teaspoon
1 to 3	0.6 to 1.2 ml.	½ to 1 teaspoon
3 to 6	1.2 ml.	1 teaspoon
6 to 12	2.4 ml.	2 teaspoons

Using body surface area as dosage gauge:

Drops	*Syrup*
8 ml./M^2/24 hrs.	33 ml./M^2/24 hrs.
Divided into 3-4 doses	Divided into 3-4 doses

MERCUHYDRIN® sodium

Using weight as dosage gauge:

Below 3 kg. — 0.125 ml.
3- 7 kg. — 0.25 ml.
7-15 kg. — 0.5 ml.
15-25 kg. — 0.75 ml.
25-35 kg. — 1 ml.

Using body surface area as dosage gauge:
1 ml./M^2/24 hrs.

QUIBRON® Elixir

Using weight in relation to age as dosage gauge:

Children under 6 — ½ teaspoon per 10 lbs. of body weight two or three times daily.

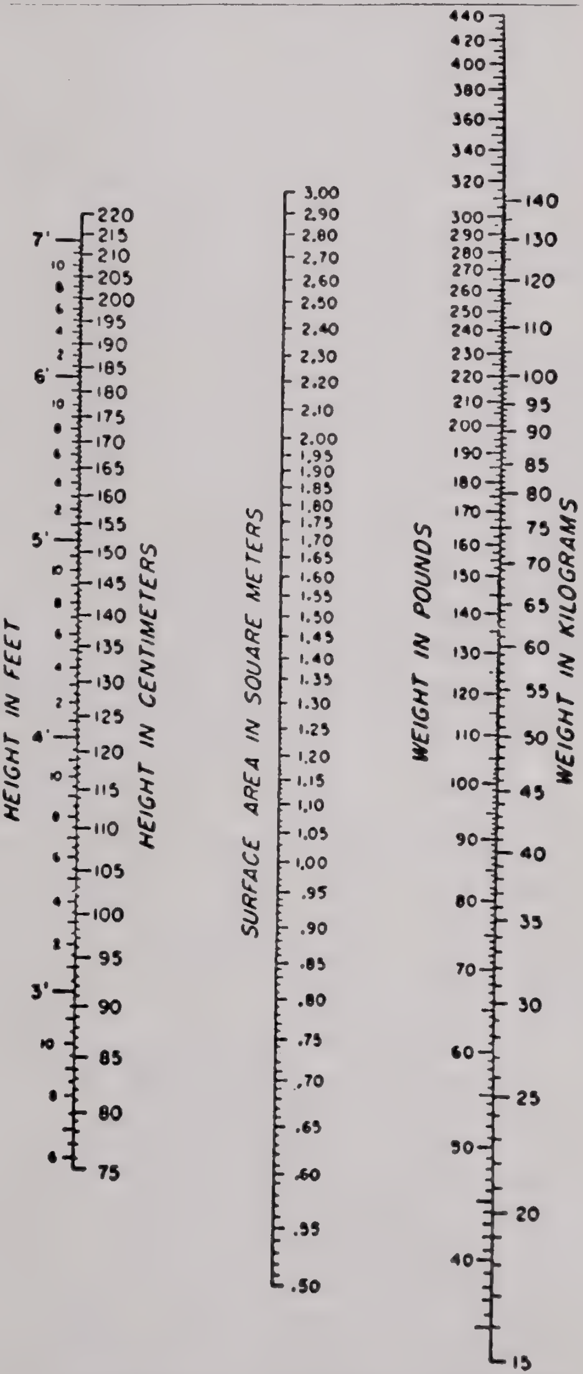
Children 6 to 12 — 1 tablespoon two or three times daily. (Note: Children weighing over 100 lbs. may require adult doses.)

Adults — 1 to 2 tablespoons two or three times daily.

Using body surface area as dosage gauge:
30 ml./M^2/24 hrs., divided into 2 or 3 doses.

Next, let us consider the application of surface area as a dosage gauge for solid

TABLE 4



Body Surface Area Nomogram for Older Children and Adults

To determine the surface area of the patient draw a straight line between the point representing his height on the left vertical scale to the point representing his weight on the right vertical scale. The point at which this line intersects the middle vertical scale represents the patient's surface area in square meters.

products:

TRIDIONE®

Using age as dosage gauge:

Infants:	300 mg.
Age 2 yrs.:	600 mg.
Age 6 yrs.:	900 mg.
Age 13 yrs.:	1.2 Gm.

Using body surface area as dosage gauge:
1 Gm./M²/24 hrs.

Piperazine Citrate

Using weight as dosage gauge:
250 mg. up to 15 lbs.
500 mg. 15-30 lbs.
1 Gm. 30-60 lbs.
2 Gm. over 60 lbs.

Using body surface area as dosage gauge:
1 Gm./M²/24 hrs.

Obviously, the relationship between dosage and body surface area is a constant in the case of most drugs. Use of this gauge would be simplified if liquid pediatric pharmaceuticals or a group of liquid pediatric pharmaceuticals were so formulated that a single dose of 10 ml. would be appropriate for a child with a surface area of 1 M².

Although solid products are less frequently used in pediatrics, particularly for infants and young children, they too can be dosed by use of surface area. For example, if a product were formulated so that the dose was 1 Gm./M²/24 hrs., a child with a surface area of 1 M² would be given 250 mg. four times a day; a child with a surface area of 0.5 M² would require 125 mg. four times a day, and so on. Obviously, small sizes of tablets would have to be available for dosage to be flexible.

Table 1 is an Equivalent Sheet showing *weight in pounds, sitting height in centimeters* (crown-rump length), *body surface area in square meters,* and *dose of liquid pediatric pharmaceuticals as above stipulated in milliliters.* Values for weights and surface areas are taken from *New Drugs,* 1966 edition.[28]

To simplify the presentation of dose information for the physician, the instructions need include only body weight along with the corresponding dose of liquids or solids. Table 2 shows how figures derived from the Equivalent Sheet could be used to give dose instructions for an imaginary product REX. In addition, a calculator or height-weight nomogram should be supplied for estimating surface area for children with unusual body configurations. Table 3 and Table 4 are DuBois nomograms.[17] Liquid products should be measured by use of a measure calibrated in milliliters and fractions of milliliters.

Comment

Use of body surface area as a gauge for dosage offers the advantages of simplicity, accuracy, and hence efficacy and safety. Obviously, the more potent the drug, the greater the need for precise dosage, the more useful is body surface area as a gauge.

Worthy of emphasis is the fact that use of body surface area as a dosage gauge does not involve a principle inherently different from that employed in using body weight. Rather, the use of body surface area represents a rational convenience. One can cite several advantages for surface area:

1. It makes it far easier for the physician to remember doses.

2. It is particularly useful in the case of drugs that are not used frequently.

3. The very simplicity of the gauge helps avoid error.

4. Once a patient's surface area is determined by whatever method, it can be used for various drugs, water, and electrolytes throughout the course of treatment.

At first glance, use of body surface area for dosing drugs appears to be a bold innovation. So did the use of the milliequivalent in place of the milligram, the metric system rather than the apothecary system, and the decimal monetary system as against the complex English pence-pound method. In science, progress is inevitable; many signs indicate that the use of body surface area as a gauge for dosage represents "the shape of things to come."

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2-30 may be secured from the author or the reprints.

For most people the hardest thing about life is the living.

Surgical Treatment of Dizziness*

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DIZZINESS IS a frequent complaint of patients seen by both the specialist and the general practitioner. Although most patients with this symptom will have a benign form of vertigo, every patient requires a thorough evaluation in order that more serious disease, such as an acoustic neuroma, may be ruled out. A small but increasing number of patients with dizziness can benefit from surgical treatment. The development and careful execution of new procedures that do not merely destroy the end organ of hearing and balance but can selectively section the vestibular branches of the acoustic nerve are possible with the operating microscope. Since the hydrops of Meniere's disease can often be relieved by shunt operations, with preservation of both the hearing and balance function of the ear, it is now desirable to treat Meniere's disease surgically in its earlier stages.

When end organ disease, excluding tumors, has been definitely diagnosed, surgical treatment of vertigo should be employed only after a reasonable trial of medical treatment has been unsuccessful. Each pathologic situation as well as the stage and severity of disease and the general condition of the patient must be carefully considered, and the surgical procedure should be selected that would best fulfill the desired result.

Conditions that produce dizziness and are amenable to surgical treatment are generally those involving the acoustic nerve or vestibular labyrinth. These conditions are Meniere's disease; vestibular neuronitis; labyrinthitis secondary to surgery, infection, or the scarring of chronic middle-ear disease; tumors of the middle ear and mastoid, and acoustic neuroma. Occasionally, trauma to the labyrinth such as the basilar skull fracture involving the semicircular canals is best treated surgically. Sometimes an ear will sustain a partial injury from a viral infection such as measles or mumps or from a vascular accident that produces persistent dizziness.

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*This paper received an award for excellence of subject matter and presentation at the meetings of the Southern Minnesota Medical Association, Minneapolis, September 10, 1965.

**Mayo Clinic and Mayo Foundation: Section of Otolaryngology and Rhinology.

Four types of surgical procedures can be employed: (1) endolymphatic subarachnoid shunt, (2) otic-periotic shunt, (3) middle fossa vestibular nerve section, and (4) destructive labyrinthectomy.

Endolymphatic Subarachnoid Shunt

Since the symptoms of Meniere's disease are caused by the increase in the endolymphatic pressure, resulting in distention of the membranes of the inner ear and stimulation of the nerve endings with ultimate deterioration of these nerve endings, this dilatation may be prevented with shunting operations. Unfortunately, it is very difficult to enter the inner ear without destroying its function. For this reason, my colleagues and I have used the endolymphatic subarachnoid shunt operation most frequently. This operation avoids the inner ear by the production of an opening through the endolymphatic sac into the subarachnoid space which is entirely posterior to the otic capsule and, although it communicates with the inner ear, the endolymphatic sac is at such a distance that a risk of a hearing loss becomes very small. Requiring approximately 1½ hours, this procedure is done with the patient under general anesthesia. The endolymphatic sac is approached through an exposure similar to that of a simple mastoidectomy; the surgeon is careful not to injure the semicircular canals. A silicon rubber shunt tube approximately ¾ inch long is placed through both sides of this sac so that one end extends into the cerebellopontine angle and is freely opened to cerebrospinal fluid (Figure 1). The other end is placed within the sac so that a continuous flow of fluid is possible from the endolymphatic sac into the subarachnoid space. The patient's usual hospital stay is six days. This procedure is successful in approximately half of the patients in relieving all of the nonpermanent symptoms of Meniere's disease. The endolymphatic sub-

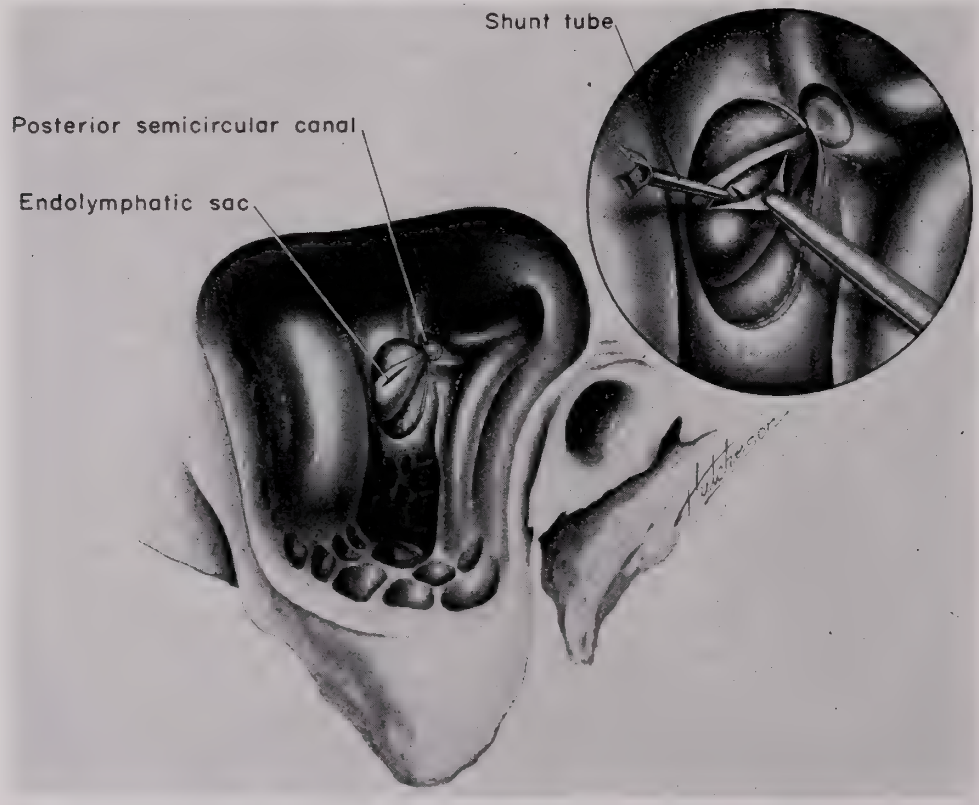

Fig. 1 — Endolymphatic subarachnoid shunt. Tube provides an opening from endolymphatic sac to cerebellopontine angle cystern.

arachnoid shunt procedure is best done when the surgeon does not wish to run any risk of making the patient's symptoms worse and when he wishes to prevent any further hearing loss or to improve the hearing situation. This procedure (1) relieves nonpermanent symptoms of Meniere's disease* in 50% of patients; (2) does not destroy the labyrinth; (3) acts to reduce all symptoms, such as fluctuating hearing loss, poor discrimination, tinnitus, pressure, and vertigo; and (4) works best when hearing is better than 50 db and fluctuates.

Otic-Perotic Shunt

Another method of producing a shunt between the endolymphatic and the perilymphatic systems can be accomplished through a standard tympanomeatal flap with the patient under local anesthesia and by an approach to the inner ear through the round window. This procedure has been called an otic-periotic shunt. Unfortunately, however, approximately 20% of patients will lose the function of the ear after this operation. Therefore, its use is reserved for patients who have very poor hearing or in whom the endolymphatic subarachnoid shunt has failed. The otic-periotic shunt has the advantage of the use of a local anesthetic and of minimal morbidity to the patient during and after surgery. Usually the patient is able to leave the hospital on the first postoperative day and has only some mild unsteadiness for about two weeks. This procedure is 90% successful in relieving the symptoms of Meniere's disease. The tiny platinum shunt tube that is pointed on one end is forced through the round-window membrane and blindly through the basilar membrane so that the shunt tube ultimately lies within the basilar membrane and allows a free flow of fluid between the scala media and the scala tympani (Figure 2). The round-window membrane rapidly heals over so that the inner ear is again sealed.

Middle Fossa Vestibular Nerve Section

Some conditions of the ear that produce vertigo involve only the vestibular portion of the inner ear so that a patient may have constant unsteadiness or recurrent episodic** vertigo but essentially no involvement of his hearing. Such conditions, when no obvious disease can be found except for dizziness and the objective caloric loss of the vestibular function of one ear, are called vestibular neuronitis. The pathology in this condition has never been clearly shown. However, it is a benign involvement of the vestibular portion of the ear. Another such situation can arise when a portion of the labyrinth is fractured. Occasionally with a basilar skull fracture or head injury the superior semicircular canal is cracked. Almost invariably, this condition cannot be detected

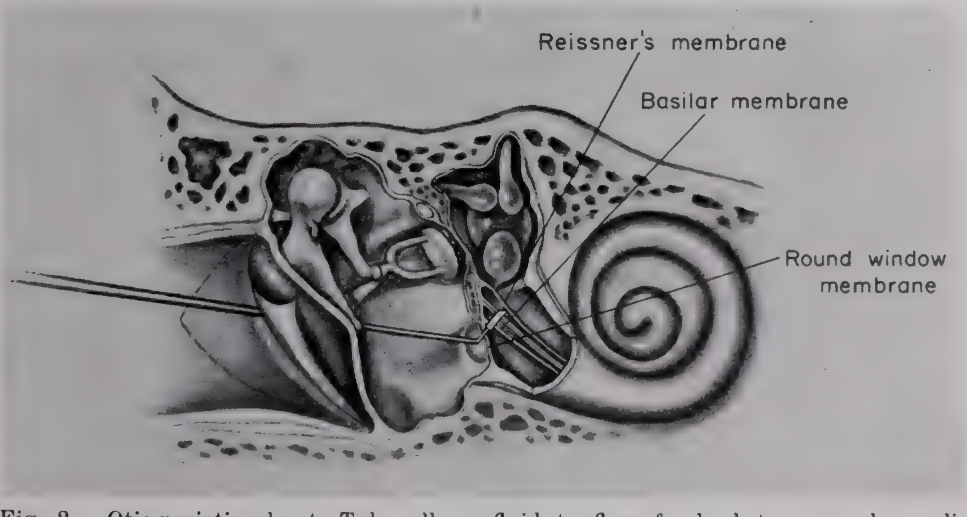

Fig. 2 — Otic-periotic shunt. Tube allows fluid to flow freely between scala media and scala tympani.

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*See Editorial page 1563.
**See Test Your Word Score, Page 1573.

by means of a roentgenogram. One can usually detect or suspect such a situation when there has been some tinnitus or slight caloric involvement or a very mild hearing loss of one ear in a patient who has had an injury associated with subsequent persistent vertigo. In most patients with fracture, the vertigo will cease spontaneously within a few months. In a few, however, the vertigo persists and is best treated surgically. Still another condition is one in which there has been long-standing chronic otitis media which, in effect, produces a very mild circumscribed labyrinthitis and irritation of the vestibular labyrinth. In this condition the hearing can be somewhat impaired. However, it would be desirable in such a case, especially when the involvement is bilateral, to preserve what hearing function there is. For these conditions, namely those basically involving only the vestibular system, the selective sectioning of the vestibular nerve through the middle cranial fossa is the treatment of choice (Figure 3). In this method with the patient under general anesthesia, an incision similar to that for the treatment of tic doloroux is made above the ear. A 1¼-inch square of bone is removed from the squamous portion of the temporal bone, and the dura of the temporal lobe is elevated with a self-retaining retractor. The greater superficial petrosal nerve is identified, and the bone covering is removed with a diamond drill. This nerve is traced to the geniculate ganglion, and the facial nerve is followed to the internal auditory canal. A small portion of bone is removed from the superior portion of the internal auditory ca-

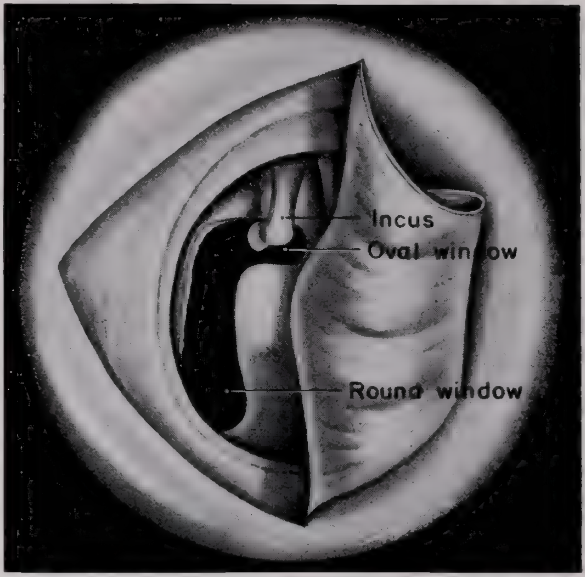

Fig. 4 — Transcanal labyrinthectomy with bone removed between windows.

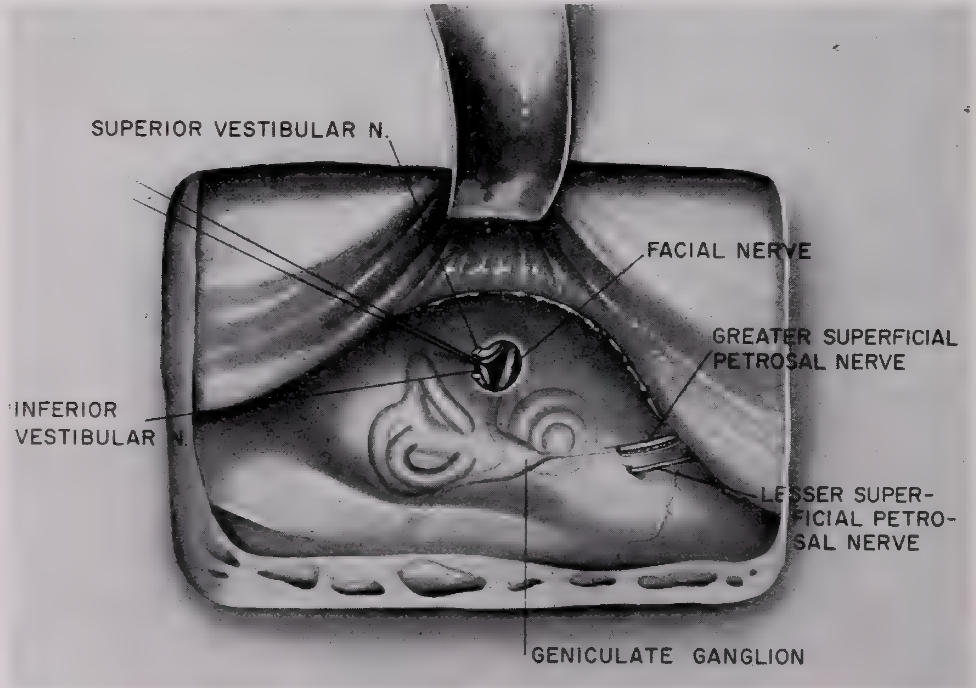

Fig. 3 — Middle fossa vestibular nerve section.

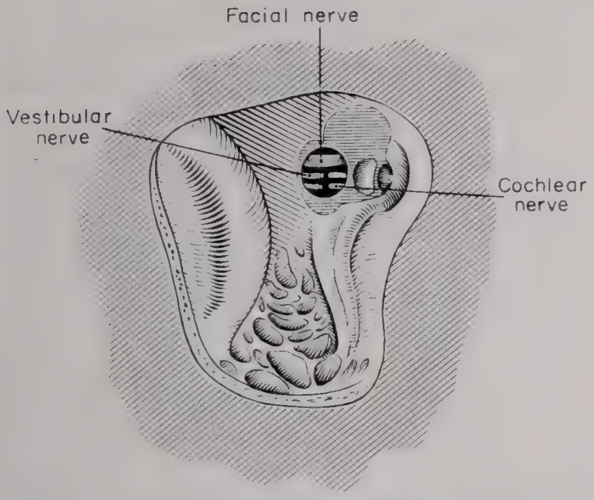

Fig. 6 — Translabyrinthine section of the eighth nerve.

nal so that both the facial nerve and the superior vestibular nerve are clearly identified. When this has been done, a hook is placed around the superior vestibular nerve and also around the inferior nerve, and these nerves are sectioned. The hospital stay for this procedure is six days, and the patient usually makes a full recovery within four to six weeks. The hearing is left unchanged.

Destructive Labyrinthectomy

Another type of surgical treatment is one that produces a destructive labyrinthectomy. This end can be accomplished in three different ways, depending on the desired results. One way is through the transcanal approach similar to a stapedectomy in which the stapes is removed and the membranous structures of the inner ear are removed with hooks and suction (Figure 4). This procedure requires a local anesthetic and is successful in removing all vestibular and cochlear function in approximately 85% of patients. Hospital stay is three or four days or until the patient is steady enough to leave. The second method is one in which more thorough labyrinthectomy can be accomplished through a postauricular incision (Figure 5). This procedure is done with the patient under general anesthesia. The bone of the mastoid is removed and the semicircular canals and posterior half of the vestibule are removed, along with the nerves to the canals. This procedure is very effective in removing all of the balance portion of the ear and is used in patients in whom

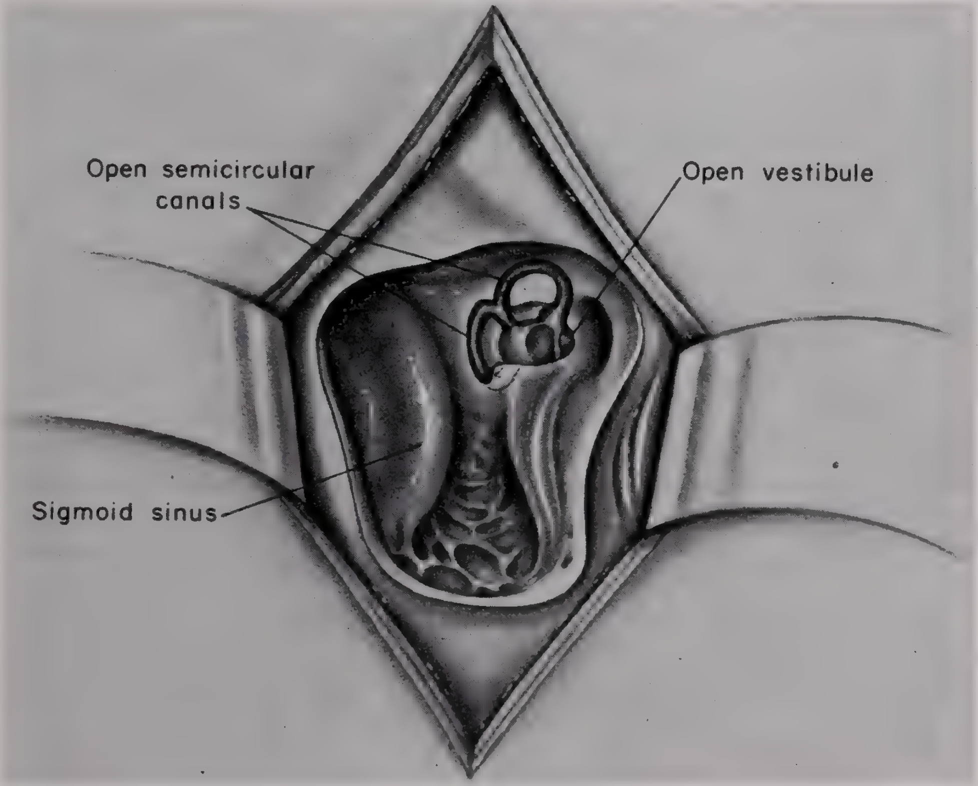

Fig. 5 — Postauricular labyrinthectomy.

scarring in the labyrinth is suspected or a previous unsuccessful procedure such as transcanal labyrinthectomy has been performed. Occasionally in a patient on whom a destructive labyrinthectomy is necessary but who complains a great deal of tinnitus along with dizziness, a translabyrinthine section of the eighth nerve is done (Figure 6). This procedure also is done with the patient under general anesthesia and is similar to a postauricular labyrinthectomy with the exception that instead of stopping the surgery after the semicircular canals have been removed, a little more bone is removed until the internal auditory canal has been exposed and the facial nerve clearly identified. A hook is then placed around the cochlear nerve, and the nerve is sectioned. If an acoustic neuroma is present, it can be safely removed, with preservation of the facial nerve. Although this method does not ensure a 100% cure of the patient's tinnitus, it is my impression from experience during the past two years that this operation offers a higher percentage of relief from noise in the head when the noise definitely results from an abnormal condition of the ear.

Summary

Surgical treatment of dizziness can be accomplished by a number of operations that selectively attack specific areas of the ear or try to accomplish certain definite change on the ear. These are: endolymphatic subarachnoid shunt, otic-periotic shunt, middle fossa vestibular nerve section, and destructive labyrinthectomy (transcanal, postauricular, or translabyrinthine section of the eighth nerve). Once a careful diagnosis has been made, the treatment must be adapted to each individual patient's need. No absolute criteria can be used for every patient who has benign disease. However, when an acoustic neuroma has been detected, it should be removed. With the judicious employment of the surgical procedures, physicians will less frequently find themselves having to tell the patient that nothing can be done for his dizziness and that he must learn to live with it.

ANGIECTID SYNDROME

This term has been used to describe a type of superficial venous lesion which appears during the first trimester of pregnancy. These vascular abnormalities occur on the posterior thigh and calf areas and consist of small, intradermal, raised, sharply circumscribed clumps of blood vessels. The areas are tender, have increased local temperature, and may be painful. They are reported to be present in approximately 10 percent of all obstetric clinic patients and are not related in any way to thrombophlebitis or to the commonplace saphenous varicosities of pregnancy.

According to Fried and associates, a distinct etiologic relationship exists between these lesions and the level of female sex hormones, more particularly with variations in the titers of serum estrogen and urinary pregnanediol. Patients with the most painful lesions show the greatest degree of estrogen or pregnanediol lack. After being present for a few weeks the lesions sometimes disappear spontaneously, but usually continue longer, often throughout the period of pregnancy and for a few weeks postpartum. Treatment consists preferably of estrogen administration in doses of 50 to 150 mg. daily. Relief of pain is usually prompt. It has been recommended that therapy be continued until the expected date of delivery.

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Dermoids of the Head and Neck

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TUMORS OF CONGENITAL origin are not infrequent entities that present problems in diagnosis and treatment. Although potential for their development is present in early embryonic life, their presence may not be apparent until long after birth.[1] Because of their insidious development they are occasionally confused with other tumors. Since these tumors may arise in obscure locations, they may become significant problems in treatment.

Some of these congenital tumors exhibit differentiation of tissues indicative of an origin from all three germinal layers, and in certain locations, notably the testis, the resulting histologic "potpourri"‡ is practically always malignant — teratocarcinoma or malignant teratoma. In the ovary, by contrast, although all three germinal layers are represented, emphasis is developed along ectodermal lines, with the resultant dermoid cyst almost always containing a large hairball and the growths being benign in 99% of cases. Mediastinal and pineal tumors of comparable type exhibit intermediate degrees of tissue complexity and incidences of malignant transformation.

Other areas of the body bear their quota of tumors which have in common a grossly cystic architecture and a lining of squamous epithelium with or without specialized adnexal structures, such as hair follicles, sweat glands, or sebaceous glands. The greatest percentage of these tend to concentrate in midline areas or in other zones wherein embryologic fusion-lines occur. Smooth-muscle strands in the walls of these cysts indicate mesodermal participation but, unlike the situation with their counterparts in the gonads, entodermal elements are almost invariably absent.

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‡See Test Your Word Score, Page 1573.

The pathogenesis of these congenital growths is a matter of controversy. Willis[2] noted that "dermoids" predominate in dorsomesial positions (spinal cord, sacral area) and about the face at the inner and outer angles of the orbit, external angular process of the frontal bone, nasofrontal sulcus, and on the cheek behind the angle of the mouth. He postulated that the tumors in these locations arose from sequestered epithelial remnants. Other authors[1,3,4] have favored an origin based on ectodermal displacement by ingrowing membranous bone. Cysts of dental origin[5] form from proliferation of paradental epithelial debris, which is "normally" present in the gums and which fails to undergo anticipated dissolution.

In many of these locations, cysts resembling dermoids microscopically but lacking a content of hair can be "acquired" by such diverse means as traumatically implanting a bit of squamous epithelium or obstructing the duct of a sebaceous gland. In these last two categories the designation "epidermoid cyst" is usually applied.

Thus it is fairly obvious that difficulties arise not only over the pathogenesis of dermoids but also over what to include in the dermoid category. For the purpose of this paper, a dermoid cyst is defined as one lined by squamous epithelium along with hair, hair follicles, sweat glands, or sebaceous glands, either alone or in combination.

Material

The cases involving dermoids seen at the Mayo Clinic during a 25-year period from 1936 to 1961 were reviewed. Dermoids involving the head and neck were the main concern; but for comparative statistical purposes those listed as occurring elsewhere in the body were studied in lesser detail. A total of 780 cases were originally screened.

In 206 cases no operation had been per-

TABLE 1
Distribution of Dermoids in the Body

Location	Number of Cases	Per Cent
Head and neck	183	33.9
Brain and spinal cord	93	17.2
Chest	59	10.9
Back	13	2.4
Abdomen and pelvis	97	17.9
Ovary	17	3.1
Testicle	2	0.4
Sacrum	30	5.5
Extremities	9	1.7
Nonspecific	38	7.0
Total	541	100.0

TABLE 3
Age at Which Dermoids of the Head and Neck Were First Noted

Age noted, yr.	Number of cases	Per cent
At birth	60	32.7
0 to 1	21	11.5
1 to 5	11	6.0
6 to 10	8	4.4
11 to 15	15	8.2
16 to 20	12	6.6
21 to 30	4	2.2
31 to 40	13	7.1
More than 40	4	2.2
Unknown	35	19.1
Total	183	100.0

TABLE 4
Dermoids of the Head and Neck: Percentage Noted at Birth and Average Age at Operation

Location	Number of cases	Percentage noted at birth	Average age at operation, yr.
Brow	58	47.6	16.2
Mouth	35	12.9	29.1
Orbit	23	35.0	21.6
Eye	15	91.7	13.2
Skull	15	58.3	17.3
Nose	14	53.8	12.3
Neck	10	30.0	18.5
Auricular	10	16.7	26.9
Lip	2	0.0	28.5
Nasolabial	1	0.0	39.0
Total	183	40.5	19.8

TABLE 5
Dermoids of the Head and Neck: Sex Distribution According to Location

Location	Males	Females
Brow	32	26
Mouth	18	17
Orbit	11	12
Eye	6	9
Skull	11	4
Nose	9	5
Neck	6	4
Auricular	4	6
Lip	1	1
Nasolabial	0	1
Total	98	85
Per cent	53.6	46.4

formed. These were immediately deleted from the survey since the clinical diagnosis could not be confirmed. In an additional 33 cases the tumors did not qualify for inclusion in the dermoid category as herein defined. Of the remaining 541 cases, those involving lesions of the head and neck were segregated for detailed study, while those in other areas were merely classified as to location. Dermoids of the head and neck accounted for 183 of the total.

Series of 183 Dermoids of the Head and Neck

Incidence and Distribution

Dermoids of the head and neck represented the largest group and constituted 33.9% of the total. The abdomen, pelvis, brain, spinal cord, chest and mediastinum constituted the balance,* as indicated in Table 1. The head and neck dermoids were distributed as detailed in Table 2. In lateralized lesions, there was a slight preponderance (70 to 57) or right-sided involvement.

Slightly more than 30% of the lesions were noted at birth, and 50% were noted before the patient had reached the age of six years (Table 3). Almost all of the tumors involving the brow were noticeable at birth.

The average age of all patients at the time of operation was 19.8 years (Table 4). The youngest patient undergoing surgery was six weeks old and the oldest 78 years of age. In both of these patients large dermoids that interfered with swallowing were present in the floor of the mouth. The younger patient also had a cleft lip.

The average age at operation varied according to the location of the lesion. In the youngest group (average age 12 years) the tumor was in the nasal region and in the

TABLE 2
Distribution of Dermoids in the Head and Neck

Location	No. of cases	Right	Midline	Left
Brow	58** (31.7)†	31	—	28
Mouth	35 (19.1)			
Tongue	0	0	0	0
Floor	35	7	25	3
Orbit	23 (12.6)	14	—	9
Eye	15* (8.2)	9	—	7
Skull	15 (8.2)			
Occipital	7	2	5	0
Parietal	2	1	—	1
Frontal	6	1	5	0
Nose	14 (7.6)			
Root	3	0	3	0
Dorsum	8	0	8	0
Tip	2	0	2	0
Columella	1	0	1	0
Neck	10 (5.5)			
High	1	0	1	0
Mid	4	1	2	1
Low	5	0	5	0
Auricular	10 (5.5)			
Pre	5	3	—	2
Post	2	0	—	2
Above	0	0	—	0
Below	3	0	—	3
Lip	2 (1.1)			
Upper	1	0	1	0
Lower	1	1	0	0
Nasolabial	1 (0.5)	0	—	1
Total	183* (100.0)	70 (37.8)	58 (31.4)	57 (30.8)

**Bilateral dermoids occurred in two cases, one brow and one eye, making a total of 185 dermoids.

†Percentage of total given in parentheses.

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*Ovarian tumors were excluded from the computation if the report of the pathologist specified a complex tridermal composition.

oldest (average age 32 years) in the lip and nasolabial area. About one quarter of all patients (25.1%) were seen after the age of 30 years, but only 17 (9.3%) had not noted the lesion by this time.

Sex Distribution

Sex distribution was likewise fairly even throughout the various areas involved by dermoids. Slightly more males than females had dermoids in the brow, mouth, nose, skull, and neck area, whereas more females had dermoids in the eye and auricular area (Table 5).

History and Clinical Observations

Sinus Drainage

A discharging sinus at one time or another was present in 17 cases (9.3%), and in six cases this was the initial symptom. Discharging sinuses were present in seven of the 14 cases of nasal dermoids; all dermoids were in the midline, and, at operation, all were found to run deeply under the nasal bones.

There were five patients who were unaware of the tumor, and it was discovered only on clinical examination or during another operation.

Infection

Acute infection in the region was the initial symptom in two cases, and pain was the only difficulty noticed in one case. Recurrent bouts of acute infection were noted in five cases. In seven cases there was a history of trauma some time before the onset of swelling or discharge; in five of these the trauma occurred in connection with a nasal dermoid.

Other Clinical Manifestations

The initial difficulty was exophthalmos in two of the cases of orbital dermoids and ptosis in another. One patient sought relief from "tongue burning" and another from "eye burning."

In one notable case, that of a 58-year-old woman whose occipital dermoid had been present since birth, the patient had no complaints and sought treatment only when her lesion had reached 18 cm. in diameter.

Some form of discomfort was present in 15 cases, varying from a "sense of pressure," a "dull ache," "occasional tenderness" to "shooting pains."

Seven patients claimed that the tumor fluctuated in size. Of the patients with sublingual dermoids, two noted difficulty in swallowing, two complained of inability to swallow properly, and one, a 59-year-old man, had such difficulty in breathing that tracheotomy was necessary to save his life.

In only four of the patients undergoing dermoid removal could a family history of any congenital abnormality be obtained. Two of these patients each had a sibling with a dermoid in the same location (brow) as they did. One patient with a pre-auricular dermoid had a sister who had undergone surgery for a branchial cyst and sinus. The mother of one patient with a brow lesion had a congenitally deformed ear.

Other congenital abnormalities were observed in 16 patients (8.7%), in six of whom multiple additional defects were noted.

In no cases was any malignant lesion reported from the site of the dermoid; however, one patient, a 39-year-old man who had had a large dermoid of his brow removed, also had a basal cell epithelioma of the root of his nose removed at the same time.

In one 59-year-old man, an epithelioma of the lower lip was removed two years after operation for a large dermoid, 5½ cm. in diameter, in the floor of the mouth. Ten years later he died of gastric carcinoma.

Pathologic Features

The dermoids varied in size from several millimeters to more than 17 cm.; the average size was 1 to 2 cm. Those in the floor of the mouth and midline of the neck averaged about 4 cm. in diameter and those on the eye, about 0.5 cm. The wall of the cyst was thick and fibrous in many cases, although occasionally a very thin wall was noted. The contents of the cyst varied from straw-colored liquid to thick, white "cheesy" material. In many cases yellow or brownish oily or pus-like material was present.

On gross examination strands of hair were noted in 43 (23.5%) of the 183 dermoids, the hair content varying according to location.

Those dermoids on the brow and scalp commonly contained hair, while there was none in the lesions on the eye.

On microscopic examination, inflammatory cells were seen in many of the dermoids. Squamous epithelium, sebaceous glands, sweat glands, hair follicles, and smooth muscle were commonly noted. In only one specimen were apocrine glands* seen. No evidence of cartilage, bone, or lymphoid tissue was noted, and entodermal elements were likewise conspicuous by their absence.

Therapy

Of all 183 patients undergoing surgical removal of the tumor at the Mayo Clinic, 40 had had an initial operation at another institution.

Surgery

Initial therapy usually consisted of incision and drainage (19 cases). In some instances this had been repeated several times; in one patient with a dermoid below the left ear no less than eight separate drainages had been performed. In one case two operations were required to completely remove a large tumor (6 cm. in diameter) in the floor of the mouth.

Needling

Other therapy included "needling" or needle aspiration, injection with sclerosing solution, and injection with antibiotics; and, in one case of a four-month-old child, a course of radiation therapy had been undertaken to cure what was thought to be a hemangioma.

Other Procedures

Secondary procedures were required in four cases: in one case, to insert an acrylic plate where a large bone defect had resulted from removal of a brow lesion; in another, to excise an "amputation-type neuroma"; and, in two cases of nasal dermoids, to use a cartilage graft to build up a defect of the nasal bridge. On four occasions nerve deficiencies were noted after operation.

Surgical Sequellae

Two patients have diplopia; one has ptosis from orbital dermoids, and another has poor visual acuity in one eye "due to retinal artery occlusion at the time of difficult surgery."

Temporary muscle weakness was noted in the orbital region in one case, and hypoglossal nerve trauma caused a tongue deviation in another.

Discussion

Various reports have placed the incidence of dermoid of the head and neck at a very low figure.[6,7] In this study it was 33.9%. One basic reason for this difference may be that, in several series, there was the inclusion of a large number of cases of dermoids from regions of the body that have been found to contain few dermoids (as they are defined in the present study).

The figure of postanal dermoids in New and Erich's[7] work was 44.48% of the total, whereas in the present study only 5.2% were found in this location.

If the ovarian and sacral dermoids are eliminated from these two series[6,7] and from the present one, the results become more compatible. The head and neck then are the predominant sites of dermoids of the body in all three series.

The number of dermoids noticed at birth varied in different sites of the body. In the neck and floor of the mouth, the number noted is not nearly so great (seven of 41 cases); most of these lesions were first noted in the second and third decade.

Perhaps this is the reason that most of the dermoids in the neck and floor of the mouth are larger than those at other sites, since they go unnoticed longer and can easily expand in the relatively soft surrounding tissue. In contrast, those about the eyes are more often noticed at birth (38 of 74 cases recorded in this study) or soon after, and are usually rather small when removed.

The length of time after the lesion was noticed and before treatment was sought seems extreme in many instances. It appears that most of the patients with small lesions are children who are brought for examination by their parents. But for most adults the time interval is much greater and cosmetic effect, fear of cancer, or discomfort of some sort is the usual reason for requesting treatment. The average age at operation for patients in this series was 19.8 years.

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*See Test Your Word Score, Page 1573.

Other congenital deformities were found in 16 of the 183 patients in this series (8.7%). These deformities varied from multiple congenital ones in five cases and a cleft lip and palate in one case to defects of a more minor nature in 10 cases. These 10 cases included two patients with hemangiomas, two with pilonidal sinuses, two with auricular deformities, one patient with a nasal defect, one with a cleft of the soft palate, one with an undescended testicle, and one with a dorsal sinus of the penis.

In Crawford and Webster's[6] series of 14 patients with nasal dermoids, two had other minor deformities. Also in the present series of 14 patients with nasal dermoids, two had minor deformities; one patient had multiple deformities of the face, urogenital system, spinal column, and extremities, and the other had a cleft lip and palate. In the series of New and Erich[7] one patient with a nasal dermoid of the septum had clefts of the upper lip, columella, and nasal tip; and Weisman and Johnson[8] reported a bilateral cleft lip and palate in which an unsuspected nasal dermoid was encountered at surgery.

The present series revealed only four cases in which congenital deformities were also present in other members of the family. In two cases of dermoids of the brow, a similar finding had been present in a sibling; the mother of a child with a large dermoid of the brow had congenital deafness in the ear on the same side as the child's defect and, in another patient with a dermoid in the left preauricular region, a sister had had a branchial sinus and cyst removed some years earlier.

In 1937 New and Erich[7] reported a mother and daughter who had identical nasal dermoids, and also a father and a son with preauricular sinuses.

Stupka[9] reported a father and daughter with similar nasal dermoids and, in 1938, Furniss[10] presented the cases of twin boys, each of whom had midline nasal dermoids.

Dermoids of the eye appear to be commonly associated with multiple congenital defects (three of five cases in this series).

The only malignancy found in this study in the same general region as the dermoids was a small basal-cell epithelioma of the nose in a 39-year-old man with a dermoid of the brow that was 2.5 cm. in diameter. The age of the patient and the site and type of cancer would lead one to believe that there was no association in the lesions. New and Erich[7] reported a squamous-cell (grade 2) epithelioma of the palate associated with a dermoid; however, in this location, chronic irritation may have been a factor and previous surgery and scarring had occurred. Many authors[7,11-13] have stated that dermoids can undergo malignant degeneration and may metastasize to lymph nodes; from this study and a review of previous cases this seems most unlikely.

Recurrence in our experience is related not to any malignant potential but to incomplete removal of the lining of the cyst. However, dermoids have been found to cause local destruction purely by their expanding properties per se.

Conclusions

A high incidence (33.9% of all dermoids of the body) was found in the head and neck. The inclusion of many ovarian and sacral lesions in other series perhaps accounted for the previously reported low figures.

All of the lesions were found to be in sites of embryonic fusion. Lesions in the most noticeable regions of the body were removed at an earlier age and were of smaller size.

The high recurrence rate is most likely due to difficulty in diagnosis of the dermoid and subsequent inadequate removal for complete cure. The difficulties in recognition of this lesion and the frequency of surgical difficulties produced by its deep extension, especially in the nasal and occipital regions, indicate a need for greater awareness of this condition.

None of the tumors in the present series exhibited a malignant potential.

References may be secured from the reprints or the author.

Reevaluation of Ileostomy Appliances and Their Application to Pediatric Patients*

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IT HAS BEEN only within the last few years that a more aggressive surgical approach has been taken toward chronic ulcerative colitis and other diseases of the colon requiring a total colectomy and permanent ileostomy in children.

Several factors are responsible for this new outlook. The most important is a realization on the part of the physician that the earlier the irreparably diseased colon is removed, the better these children do in growth and social adjustment. The improvements in pediatric anesthesia and in preoperative and postoperative care have contributed greatly.

The major contribution to postoperative care has been the evolution of a "better mouse trap," so to speak, in the form of a better appliance. There are many commercially available appliances. Practically all depend on some type of adhesive to hold the appliance in place. Many are also bulky, odorous, and leaky (causing skin irritations), and they are quite complicated to assemble, particularly for a child. The magnitude of ileostomy problems was studied by McNamara and Farber,[1] who sent questionnaires to 1,048 patients including children and adults. Seventy-nine per cent had some sort of circumileostomy difficulty, mostly due to ill-fitting appliances and use of adhesives.

Because of the many drawbacks and problems, we searched around for a more suitable appliance. We are now using the Robinson ileostomy appliance at the Mayo Clinic.

Construction of Appliance

This is an extremely simple device, designed by the late Mr. Herman Robinson of Seattle, Washington, around 1958.[2] Steven-

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*Read at the meeting of the Southern Minnesota Medical Association, Minneapolis, Minnesota, September 10, 1965.

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†Mayo Clinic and Mayo Foundation: Section of Surgery.

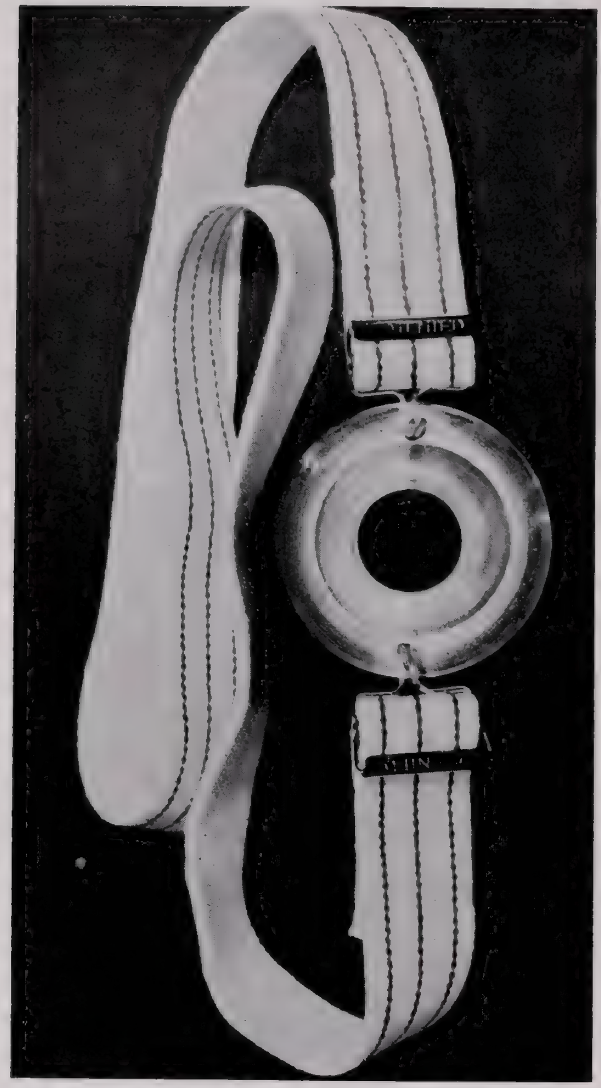

Fig. 1 — Appliance with belt attached.

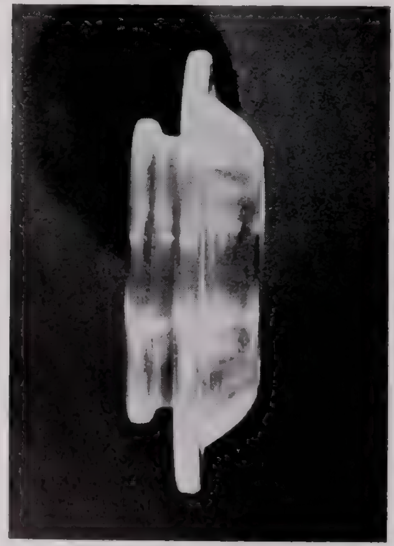

Fig. 2 — Lateral view of appliance.

son and Volwiler[3] at the University of Washington were the first to use the appliance on a large scale. This appliance consists of a plastic disk which is convex on the skin side. When the belt is attached, the convex surface presses against the skin surrounding the stoma and causes the stoma to protrude into the ring (Figures 1 and 2). This creates a seal which will not allow odors or liquids to escape. No adhesives are used. A Saran plastic bag is attached to the disk by turning the bag inside out, inserting the disk inside the bag, and applying a rubber band (Figure 3). An opening is made in the bag by use of a fingernail file or small scissors (Figure 4). The bag is then turned right-side out and a rubber band is applied to the distal part. It is now ready for wear (Figure 5).

Stomal Location

The stomal location is of utmost importance in fitting an appliance. The surest way of putting the ileostomy in the proper place is to have the patient wear the appliance for a day or so preoperatively to decide exactly where it fits best. This also has some psychologic benefit in that he is deciding himself where the permanent location will be. Figure 6 shows one of our patients wearing the appliance preoperatively; he had suffered from severe chronic ulcerative colitis with secondary arthritis of the left knee. He previously had undergone a partial colectomy and ileoproctostomy. He returned because of ulcerative colitis involving his rectum. He later named his stoma "Cyclops" because, he said, it had just one eye.

The night before operation the skin is scratched in the center of the disk, and the stoma is located at that site at the time of surgery. Ideally, the stoma should be constructed so that it protrudes 2½ to 3 cm. above the abdominal wall. We prefer the Brooke-type ileostomy.

Postoperative

A Bongort plastic adhesive bag is applied at the time of surgery. Seven to ten days postoperatively, when the mucocutaneous areas appear healed and most of the stomal

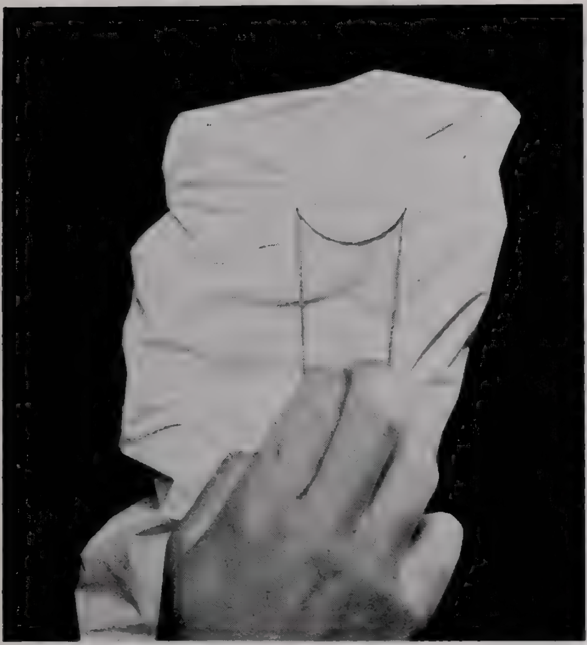

Fig. 3 — Attachment of bag to appliance.

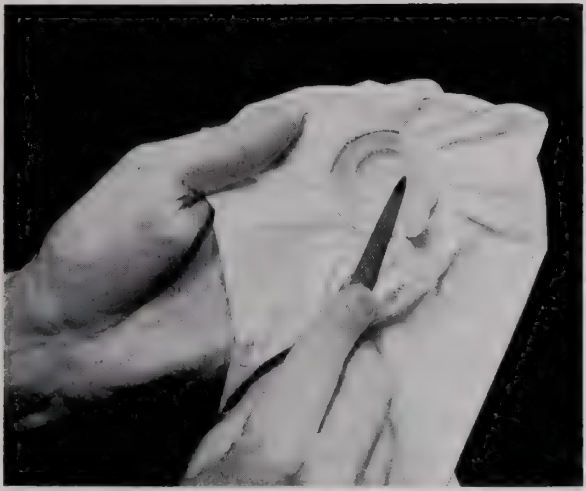

Fig. 4 — Creating opening in bag.

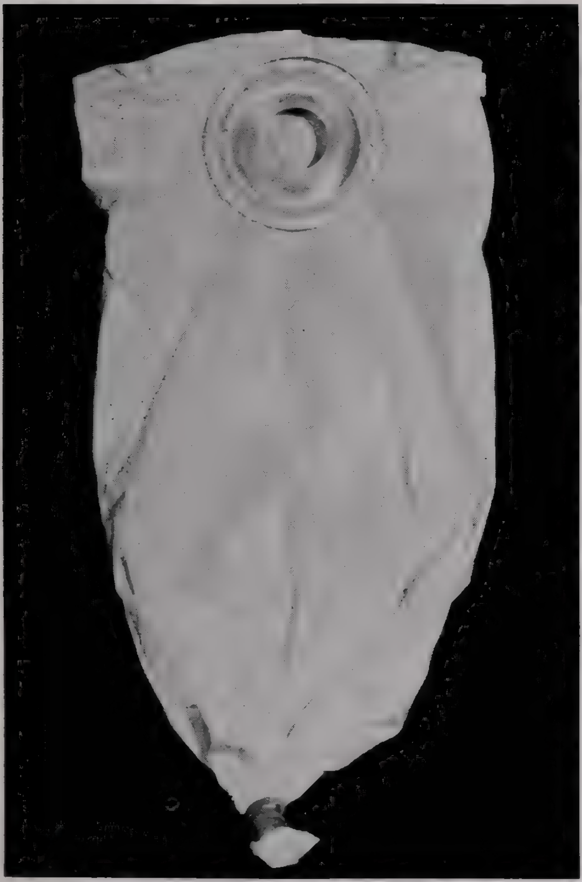

Fig. 5 — Appliance ready for wear.

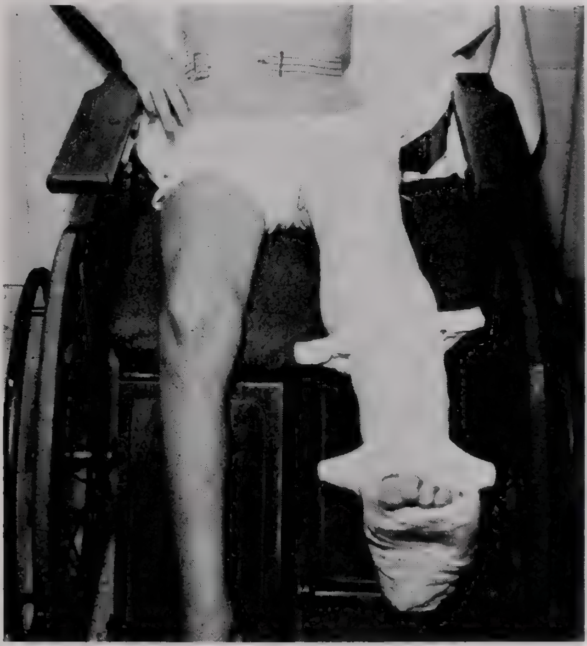

Fig. 6 — Preoperative fitting.

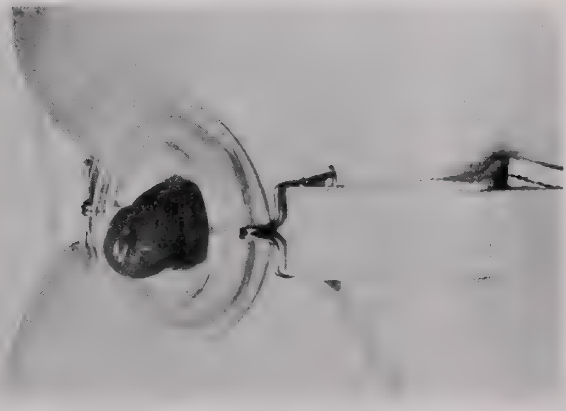

Fig. 7 — Appliance is fitted postoperatively.

edema has subsided, the diameter of the stoma is measured by use of a caliper. An appliance is then fitted that leaves approximately an eighth of an inch of skin exposed around the stoma (Figure 7). It may be necessary to convert to a smaller-size appliance at a later date if stomal shrinkage occurs.

Complications

To date we have used the Robinson ileostomy appliance in children ranging from 8 to 15 years of age. We have fitted several children who had their ileostomies performed elsewhere but because of ileostomy and appliance difficulties were seen at the Mayo Clinic. There have been no problems with leakage, odor, or skin breakdown. Because of its simplicity, practically all children are able to take care of their own appliances. Our only complication occurred in a boy who rubbed a raw area on the lower side of the stoma while playing football. At a later date, while playing basketball, he actually broke one of the eyelets to which the belt attaches. Many of our patients are active in various forms of athletics, including swimming.

Summary and Conclusions

Stomal location is extremely important in proper fitting of an ileostomy appliance and when possible should be decided on preoperatively.

The Robinson ileostomy appliance has been used in children ranging from 8 to 15 years of age at the Mayo Clinic. There have been no problems with odor, leakage, or skin breakdown.

The pursuit of a normal childhood has been made possible, including participation in all types of athletics.

The ileostomy appliance is the problem and the responsibility of the surgeon. While any patient with an ileostomy soon learns more about its management than his surgeon knows, it is not fair for the surgeon to turn his back on these patients and expect ileostomy clubs, surgical supply houses, family, and neighbors to bear the full responsibility for having these patients adjust to their problems. Many patients will lead lives of misery because of poorly fitted appliances. The Robinson ileostomy appliance has made this situation much more tolerable, and it is our impression that youth itself is also a great aid in this period of stress.

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IT'S THE LAW

The present position of the state welfare department demanding that the doctor accept assignment of benefits is a departmental directive and *not* a law. The welfare board is required by law to pay the medical expenses of their clients. The welfare board is the prime contractor for medical services to their recipients and is, therefore, directly responsible for their medical expenses. Any arrangement of the welfare board with a third party such as Medicare is their particular concern and not a concern of the medical profession. The contract is between the welfare board and Medicare, and the physician is not involved.

One Man's Meat

In some other countries, where conditions of living are entirely different from those in the United States, problems of health have been solved by socialization of medicine, but to assume that we should imitate those solutions is ridiculous.—Charles Mayo

Obstruction to Left Ventricular Outflow*

Functional and Clinical Considerations

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Obstruction to the flow of blood from the left ventricle can exist either below, at, or above the aortic valve. Thus there may be subaortic, valvular aortic, or supravalvular aortic stenosis. The purpose of the present paper is to correlate the functional and clinical manifestations of these three levels of obstruction with the basic mechanisms of each.

Basic Considerations

Subaortic, valvular aortic, and supravalvular aortic stenosis share in common the fundamental disturbance of an obstruction to the forward flow of blood, the obstruction requiring that the pressure be increased proximally to maintain flow. A pressure gradient can therefore be recorded as the catheter tip crosses the stenotic area. The relationship between the variables — blood flow, pressure gradient, and severity of stenosis can be seen from the statement that flow is proportional to orifice size and the square root of the pressure gradient.[1]

Similarities between the Various Types of Left Ventricular Outflow Obstruction

The left ventricle hypertrophies as a consequence of the increased work load imposed by the stenosis. With the exception at times of idiopathic hypertrophic subaortic stenosis, the hypertrophy is usually concentric, and in the absence of left ventricular failure the cardiac silhouette is generally not enlarged by roentgenography. For this reason hypertrophy can often be better appreciated from the electrocardiogram than from the roentgenogram. Marked left ventricular hypertrophy can produce electrocardiographic patterns resembling those seen in myocardial infarction; but these changes are perhaps more often seen in muscular subaortic stenosis where there is an extreme hypertrophy of the interventricular septum.

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A similar symptomatology is seen in subaortic, valvular aortic, and supravalvular aortic stenosis. This includes dyspnea, angina, syncope and heart failure. The onset of any of these symptoms is of ominous import.

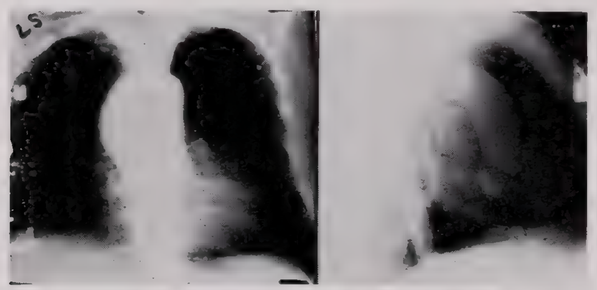

Fig. 1 — Retrograde supravalvular aortogram of a 53-year-old man with both severe calcific aortic valvular stenosis and severe coronary arterial disease. Left: posteroanterior view. Right: Lateral view. Note the negative jet of blood squirting through the stenotic valve during ventricular systole, and the post-stenotic dilatation of the aorta. The coronary arteries are also diseased.

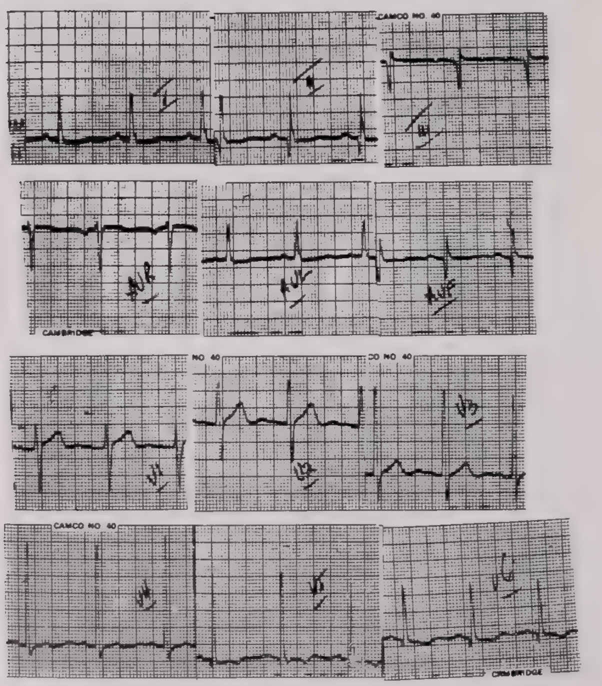

Fig. 2 — Electrocardiogram of the same patient as in Figure 1. The deep Q and abnormal T waves in Leads II, III, and aVF indicate an old posterior myocardial infarct. However, the tracing fails to show good evidence of the additional presence of severe aortic valvular stenosis.

Decompensation occurs when the left ventricle can no longer sustain its work load and is associated with a high left ventricular mean diastolic pressure. The pressure is also elevated in the left atrium and proximally. An elevation of pulmonary venous and capillary pressure above a critical value produces pulmonary edema. This sequence of events explains the symptoms of dyspnea and congestive failure.

At the same time that congestion occurs upstream to the obstruction, there is interference with the forward flow of blood. A reduction in the cardiac output and the diminished perfusion of the brain can result in faintness and syncope, events most likely appearing when the patient assumes the erect position, since the heart must then overcome the highest column of blood in order to nourish the brain. The combination of decreased cardiac output and increased left ventricular work, together with hypertrophy, accounts for the presence of angina pectoris.

The final condition that is shared by patients with these lesions is sudden death, a dread event that can occur even while the patient is asymptomatic.

Dissimilarities Between the Various Types of Left Ventricular Obstruction

Although subaortic, valvular aortic and supravalvular aortic stenosis share some findings as described above, there are also interesting differences. These dissimilarities occur because of the difference in the level of the obstruction, because of some special characteristic of the basic lesion, or because of different defects or conditions which occur in association with the basic lesion. These features can best be discussed by individually considering valvular, supravalvular and subvalvular aortic stenosis.

Valvular Aortic Stenosis

Valvular aortic stenosis is the most common form of left ventricular outflow obstruction.[2,3] The usual etiology is rheumatic fever, although congenital stenosis does occur. Aortic valvular stenosis is seen more frequently in men than in women.

Typically there is a coarse ejection murmur at the base which often radiates along the carotid arteries.[4] A systolic thrill may also be palpable. The aortic closure sound is usually diminished or absent, but is occasionally present even when the stenosis is severe. The second heart sound may be single; occasionally it may split paradoxically, in which case the aortic closure sound follows the pulmonic closure sound. This effect is probably due to the prolonged left ventricular ejection period produced by the stenosis. An ejection click may be heard especially at the base, and a fourth heart sound is sometimes audible at the apex. An aortic valve which is stenotic may also be incompetent.

Roentgenograms may show valvular calcification. Poststenotic dilatation occurs principally in the ascending aorta. Aortography may show a ragged border to the valve and a negative jet of blood squirting through the stenotic orifice (Figure 1).

The aortic pressure pulse usually shows a slow ascending limb which may have an anacrotic* notch. Typically the pulse pressure is small. Aortic stenosis is occasionally associated with systemic hypertension.

Severe aortic stenosis complicated by severe coronary arterial disease can be a difficult diagnostic problem. Angina pectoris, dyspnea, and heart failure can occur with either condition, and the electrocardiographic findings may not be clear-cut. The patient whose aortogram is shown in Figure 1 was such a case. He had severe angina, angiographic evidence of coronary arterial disease, and severe calcific aortic stenosis confirmed at surgery. His electrocardiogram (Figure 2) showed evidence of an old posterior myocardial infarct, but little that was suggestive of his valve lesion.

Supravalvular Aortic Stenosis

Supravalvular aortic stenosis can occur either alone or as part of a syndrome. The belief has been that the isolated lesion occurs more frequently, but recent proposals have suggested that more commonly it is part of a syndrome, the other features of which may not be clearly in evidence or may even be absent.[5]

The area of the stenosis can be visualized by angiocardiography. Figure 3 is an example of a patient with supravalvular aortic stenosis together with tubular aortic hypoplasia. A pressure gradient can be recorded as the catheter tip is withdrawn across the supravalvular stenotic area, as demonstrated in Figure 4. In contrast to aortic valvular stenosis where the coronary arteries arise downstream to the area of obstruction, in supravalvular aortic stenosis the ostia of the coronary arteries are proximal to the level of the obstruction. The coronary arteries are therefore subjected to the same elevation in systolic pressure as is the left ventricle, which probably accounts for the dilated appearance the coronary arteries may show in this condition.

A systolic ejection murmur is usually heard at the right upper sternal border and a systolic thrill may be present. The amplitude of the aortic closure sound is normal. Aortic diastolic murmurs are absent. The blood

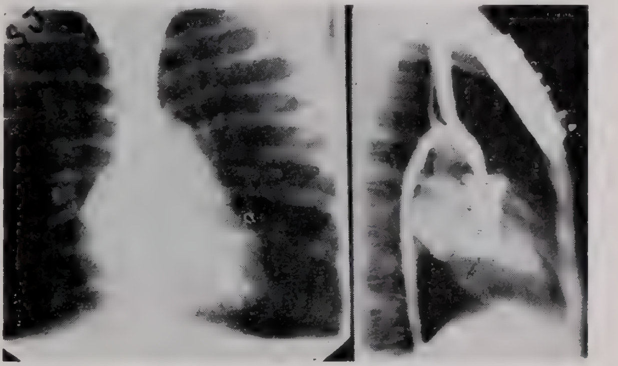

Fig. 3 — Retrograde supravalvular aortogram of a patient with supravalvular aortic stenosis. Left: posteroanterior view. Right: Lateral view. There is severe supravalvular aortic stenosis and tubular aortic hypoplasia.

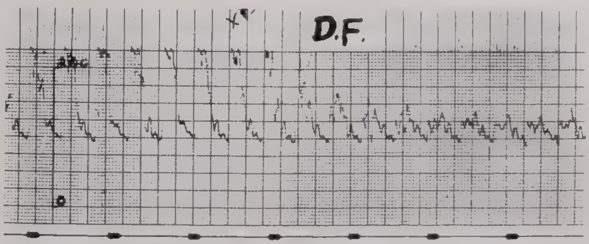

Fig. 4 — Withdrawal pressure tracing across the stenotic area of a patient with supravalvular aortic stenosis. A marked decrease in systolic pressure is recorded as the catheter tip is withdrawn across the area of supravalvular aortic stenosis into the aorta downstream to the obstruction.

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*See Test Your Word Score, Page 1573.

pressure in the right arm is commonly higher than that in the left. This may be due to hypoplasia of the aortic arch branches or to the impact of the jet of blood caused by the obstruction.

Supravalvular aortic stenosis can comprise a part of a syndrome that in addition includes mental retardation, a characteristic facies, peripheral pulmonary artery stenosis and, in infants, hypercalcemia. As discussed by Jue and associates,[5] a patient may demonstrate all or some of the features which go to make up the complete syndrome. Figure 5 reproduces the pulmonary arteriogram of a patient with peripheral pulmonary artery stenosis as well as supravalvular aortic stenosis. Figure 6 shows the pressure tracing as the catheter tip is withdrawn from the pulmonary artery wedge position to the main pulmonary artery. A pressure gradient is evident as the catheter passes from the distal pulmonary artery segment, where the pressure is lower, across the stenotic area into the higher pressure segment proximal to the obstruction. The combination of supravalvular aortic stenosis and right ventricular or pulmonary arterial hypertension should alert one to the probability of peripheral pulmonary artery stenosis, especially if other features of the syndrome are present.

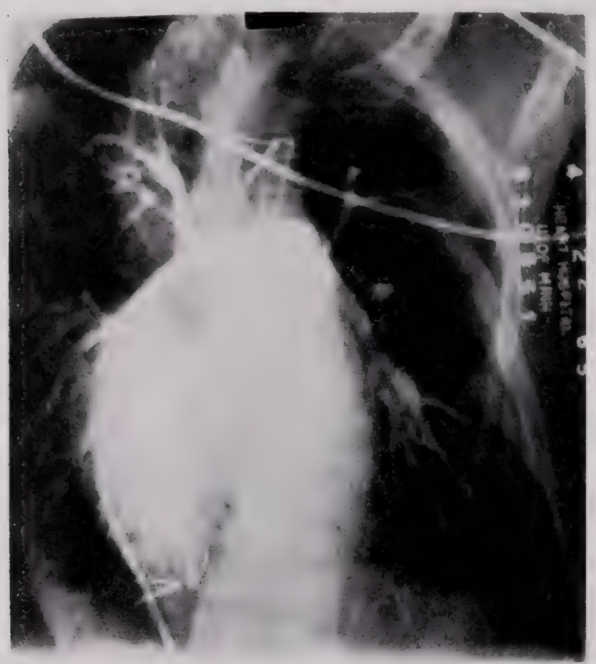

Fig. 5 — Pulmonary arteriogram of a patient with supravalvular aortic stenosis. There are multiple sites of peripheral pulmonary artery stenosis. Some vessels show post-stenotic dilatation.

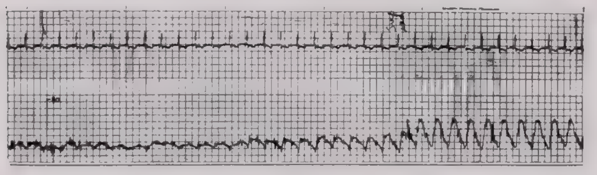

Fig. 6 — Continuous withdrawal pulmonary artery pressure tracing in a patient with peripheral pulmonary artery stenosis and supravalvular aortic stenosis. At the left the catheter tip is in the pulmonary artery "wedge" position and a normal venous type pressure is recorded. As the catheter is withdrawn, a pulmonary artery pressure of low amplitude is first seen. There is then an abrupt increase in systolic pressure as the catheter tip crosses the area of peripheral pulmonary artery stenosis and enters the segment of pulmonary artery proximal to the obstruction.

Subaortic Stenosis

Edwards has discussed the conditions which can produce subaortic stenosis.[2] All will show a pressure gradient across the obstruction as a result of the impediment to the forward flow of blood. Figure 7 shows the pressure gradient recorded in a patient with idiopathic hypertrophic subaortic stenosis. This variety of subaortic stenosis displays characteristic features not shared by the other types and caused by the dynamic nature of the obstructive process.[6] The stenosis results from the encroachment of septal and left ventricular muscle into the outflow tract of the left ventricle. During ventricular systole this muscular mass also contracts, constricting the outlet; in diastole the left ventricle relaxes and expands as it fills with blood. This explains why little or no narrowing of the outflow tract occurs in diastole.

Idiopathic hypertrophic subaortic stenosis is associated mainly with two other findings. Anatomic changes may occur in the mitral valve with resultant mitral insufficiency. Also hypertrophy of the wall of the right ventricle and interventricular septum will at times produce a similar dynamic obstruction in the right ventricular outflow tract.

Because of the muscular nature of the obstruction, variability is a characteristic feature in idiopathic hypertrophic subaortic stenosis. The magnitude of the obstruction and hence of the pressure gradient may vary and, indeed on occasion, an obstruction cannot be detected. Methods are available which will induce, increase, or abolish the systolic pressure gradient. These methods perhaps operate by altering the force of myocardial contraction, or the ventricular systolic volume, or both. It has recently been suggested[7] that the pressure gradient in idiopathic hypertrophic subaortic stenosis may not be related to an actual left ventricular outflow obstruction. According to this interpretation a segment of ventricle completely expells its contents in early systole. The high ventricular pressure is then produced by the continued systolic contraction of this portion of the ventricle about the catheter tip.

The systemic arterial pressure pulse often exhibits a characteristic contour. The upstroke of the pulse is more rapid than normal. In mid-systole there is a dip in the arterial pressure which paradoxically coincides with the point when the peak pressure is reached in the left ventricle. As the pressure in the left ventricle falls, a secondary rise in arterial pressure follows the preceding dip. The systemic arteries do not show this notched systolic contour in valvular aortic or discrete subaortic stenosis.

The response of the beat following a premature ventricular contraction has been found to be helpful in the diagnosis of idiopathic hypertrophic subaortic stenosis. The post-extrasystolic beat is associated with a widened peripheral arterial pulse pressure in the normal and in patients with valvular aortic and discrete subaortic stenosis. In idiopathic hypertrophic subaortic stenosis the response of the post-extrasystolic beat is abnormal in that the pulse pressure is the same as or less than that of the regular control beat. This is illustrated in the right hand panel of Figure 7. Patients with this disorder who at the moment have no detectable pressure gradient may develop a large gradient with the post-extrasystolic beat.

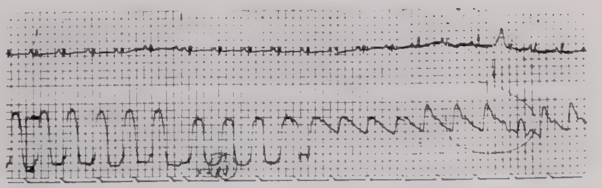

Fig. 7 — Discontinuous left ventricular, aortic, and brachial artery pressure tracings from a patient with idiopathic hypertrophic subaortic stenosis. Left: Left ventricular pressure tracing with the catheter tip positioned toward the apex. Center: Withdrawal pressure tracing from the outflow tract of the left ventricle to the aorta. There is a small systolic pressure gradient between the apex and outflow tract of the left ventricle but none across the aortic valve. Right: Brachial artery pressure tracing. The fourth beat from the right is a premature ventricular contraction. The pressure pulse associated with the post-extrasystolic beat shows a prominent mid-systolic dip in the pressure and a pulse pressure which is less than that of the control beats. The beat following the post-extrasystolic contraction still shows a visible, though smaller, mid-systolic dip in the pressure. These features are considered typical of idiopathic hypertrophic subaortic stenosis.

A systolic murmur is almost always present in idiopathic hypertrophic subaortic stenosis, sometimes accompanied by a thrill. In contrast to the other forms of left ventricular outflow obstruction where the murmur is located more at the base, in this condition the murmur is usually at the left sternal border or at the apex. A paradoxical splitting of the second heart sound and a fourth heart sound may be noted.

Roentgenographic examination may also be helpful. Cardiomegaly may be present. Aortic valvular calcification is absent, and dilatation of the ascending aorta is not present or is minimal.

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Progress is just the slow business of falling in line with the schemes of minorities. — Wheeling Intelligencer

WHAT'S YOUR DIAGNOSIS?

A 60-year-old white female presented herself in her doctor's office complaining of abdominal discomfort for the past three weeks. She described her distress as a constant, "gnawing pain," located in the epigastric area with occasional radiation or spread to the right subcostal area. The pain was not related to or relieved by food. Stools were regular but for two weeks had been pale yellow in color. No weight loss had been noted. The past medical history was negative; she had never had an operation. She smoked about one package of cigarettes a day and used alcohol moderately. Examination revealed a healthy white female. The liver edge was palpable three centimeters below the right costal margin. Ascites was suspected, but the remainder of the examination was negative. No jaundice was noted and serum bilirubin was 0.83 direct, 0.81 indirect, total 1.64 mg%. An upper G.I. study and cholecystogram were normal. There was no anemia.

The epigastric pain remained constant but became more severe. There was no back pain. She was admitted to the hospital six weeks after the onset of her first symptoms. She then complained of abdominal bloating, enlargement of the abdomen and anorexia for two weeks. Jaundice was noted on her admission examination. The liver edge was down six centimeters and was tender. Shifting abdominal dullness was observed. No telangiectases were found. Proctoscopic examination was negative. Barium enema examination was normal.

Laboratory data: Hgb. 14.1 Gm%
wbc. 6470
Urinalysis negative
Prothrombin activity 56% of normal
BUN. 6.25 mg%
Serum bilirubin direct 3.2
indirect 1.4
Total 4.6
Alkaline phosphatase 9.7 King Armstrong units
Serum transaminase 113 units (normal range 10-40 units)
Sedimentation rate 34 mm/hour
Stool for occult blood — trace
LDH 195 units (normal range 60-120)
Cephalin flocculation negative at 24 and 48 hrs.

The consultant agreed that abdominal exploration and liver biopsy was indicated. Ten days after admission the abdomen was explored.

What's Your Diagnosis? Turn to page 1559.

Gulliver's Travels — Jonathan Swift*

Gulliver — On Wine

"Wine was not imported among us from foreign countries, to supply the want of water or other drinks, but because it was a sort of liquid which made us merry, by putting us out of our senses; diverted all melancholy thoughts, begat wild extravagant imaginations in the brain, raised our hopes, and banished our fears; suspended every office of reason for a time, and deprived us of the use of our limbs, until we fell into a profound sleep; although it must be confessed, that we always awaked sick and dispirited; and that the use of this liquor filled us with diseases, which made our lives uncomfortable and short." — Heritage Press, 1940.

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*See Minnesota Med 49:1368, 1966.

On Quaffing

The trouble with people who drink like fishes is that they don't drink what fishes drink. — Louisville Courier-Journal

Antihypertensive Therapy in Clinical Practice

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THIS STUDY was undertaken in order to evaluate the effectiveness, benefits, and complications of antihypertensive therapy in an unselected group of patients as seen in the private practice of internal medicine. It is felt that much of this study's significance relates to the clinical realism of its conditions: an unselected group of hypertensive patients examined and treated in standard clinical surroundings.

Reports of a number of recent studies have recommended polythiazide[**] for long-term management of hypertension and its attendant disorders, with minimal incidence of side effects and complications.[1-6] This drug, therefore, was selected to initiate therapy.

Methods and Materials

Patients

Fifty-two patients were chosen at random from a private office practice. Two were dropped from the study because of possible drug reactions. In the remaining 50 patients, there were 21 females and 29 males, ranging in age from 34 to 75 years. The majority had had hypertension of long standing and had been referred as failures on previous treatment. Thirty-two of the 50 had been treated with an agent other than polythiazide prior to this study; 18 patients had not been treated previously.

A minimum diastolic pressure of 100 mm. mercury was recorded on at least two examinations before each patient was included in the study group. The patients were then classified in three groups according to the severity of hypertension indicated by blood pressure:

Mild (100 to 109 diastolic)	Eight patients.
Moderate (110 to 119 diastolic)	Eighteen patients.
Severe (120 diastolic)	Twenty-three patients.

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[*] Mesaba Clinic

[**] Supplied as Renese, by the Medical Department of Pfizer Laboratories.

Eight patients had definite cardiac, renal, or cerebral complications prior to the initiation of therapy. (See Table 1.)

TABLE I

Myocardial Infarctions	Recent	2
Myocardial Infarctions	Old	2
Cardiac Failure	(At Onset of Treatment)	1
Cerebral Vascular Accidents		2
Chronic Renal Disease	(Elevated BUN.)	1

Clinical Studies

On each patient's visit a general physical examination was performed with special attention to evaluation of the eyegrounds, character of peripheral pulses, presence of abdominal or cervical bruits and cardiac examination. Patients were closely questioned as to family, history of cardiovascular disease, diabetes or gout, cerebral, renal or cardiac symptoms. Each patient was examined on at least two occasions before antihypertensive therapy was initiated. The patients were then seen at intervals consistent with the severity of their blood pressure and their response to medication. On each subsequent visit the blood pressure was taken in both arms in the sitting position, also in the standing position in any patients taking sympatholytic drugs.

Laboratory Procedures

Routine tests performed at the beginning of therapy for each patient covered c.b.c. and urine, chest x-ray, EKG., BUN., cholesterol, and fasting blood sugar. Uric acid was also examined and a colorimetric screening test* used to detect urinary infections. All blood pressures were taken by the investigator; all laboratory work was performed consistently by the same technicians. Qualified radiologists interpreted the chest x-rays, and a single observer read all electrocardiograms. (See Table 2 for previous therapy.)

Treatment of Hypertension

The initial dose was either 1 or 2 mg. of polythiazide per day, as determined by the severity of the blood pressure. This dosage was subsequently increased, when necessary, to a maximum of 4 mg. daily. If optimal blood pressure control was not achieved within 30 days, a second drug was added to the program — usually guanethidine** or methyldopa.†. A Rauwolfia compound was also found to be a very useful second drug when anxiety or tension played a significant role in a case. When adequate control of the hypertension had been maintained for two to three months, the drug dosages were decreased at two or four-week intervals, until the minumum dosage necessary to maintain control was reached. Diets were instituted for overweight patients, and all patients were instructed to follow a one-gram sodium diet.

The criterion used to evaluate the results of therapy was diastolic pressure. When this was 90 mm. mercury or lower, the result was considered excellent; between 91 and 100, fair, and over 100, poor.

Results

Of the total 50 patients, 43 (or 86%) showed excellent response to therapy; seven patients (14%) had fair response; there were no poor results.

A fall in diastolic pressure was noted in all 50 patients, the average fall being 26 mm. mercury. In addition, a significant drop in systolic pressure was noted for all 50 patients, an average drop of 50 mm. mercury.

In 12 cases it was possible to reduce the polythiazide dose while retaining control of blood pressure. This reduction was quite impressive in many patients who initially required 4 mg. daily and were eventually controlled on ½ mg. every other day. In two patients the drug was stopped for a period of two months with no rise in blood pressure during that period. Subsequently, a rise in blood pressure required very small doses of polythiazide. One patient, who developed diabetes mellitus during the treatment period and who was in cardiac failure prior to treatment, has remained out of failure and controlled for a period of four months after discontinuing polythiazide.

Twenty-five patients were maintained on 4 mg. of polythiazide, 10 patients on 2 mg., nine on 1 mg., and five on less than 1 mg. daily.

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*Uroscreen, Charles Pfizer and Company.

**Ismelin

†Aldomet

Nine patients required additional hypotensive agents due to inadequate control. (See Table 3.)

In three patients with original cardiac enlargement, there was a decrease in cardiac size demonstrable by x-ray. In four patients there was definite improvement in electrocardiograms.

An initial rapid loss of three to eight pounds was a usual finding; however, this weight was frequently regained over the next two to three weeks. Twenty-nine patients lost an average of 16 pounds over the entire study period; six gained an average of eight pounds, and 15 experienced no weight change.

Side Effects and Complications

In general the drug was very well tolerated. When large doses of polythiazide were used initially, malaise, weakness and rapid weight loss were common findings. However, if smaller doses of the drug were used initially, followed by an increase in dose, characteristic weight loss occurred more slowly and symptoms were negligible. The most efficacious initiating dose was 2 mg. for severe hypertension and 1 mg. for mild to moderate elevations of blood pressure.

Two patients were dropped from the study because of initial side reactions. The first reaction consisted of a rather ill-defined syndrome of tingling extremities, malaise, and weakness associated with impotence. The second patient, who had a chronic neurodermatitis prior to therapy, developed a generalized maculopapular* eruption that was resistant to therapy. Both of these reactions cleared after cessation of polythiazide. However, the investigator did not feel it prudent to challenge these two patients with the drug at a subsequent date.

There was a rather surprising increase in uric acid in 56% of the group, the average increase for the 28 patients being 2.41 mg. However, only two patients experienced any joint symptoms, obviously gout. One of them had had gout prior to initiation of polythiazide. Both were rather easily controlled by probenicid and colchicine, plus a diminution of the polythiazide dose. There was no increase in cholesterol accompanying the uric acid elevations. Two patients required potassium supplements because of symptoms referable to hypopotassemia.

Frank diabetes appeared in two patients, both of whom had normal blood sugars prior to therapy. The first of these patients, a 65-year-old white male with moderate hypertension, had an excellent response to polythiazide, his systolic pressure falling 40 mm. mercury and his diastolic pressure 15 mm. mercury. There was also a weight loss of 20 pounds. Thirteen months after initiation of therapy, glycosuria was noted; blood sugar was found to be 300 mg. per cent. Polythiazide was then discontinued and chlorpropamide** instituted. The diabetes was easily controlled and, interestingly, the patient's blood pressure remained under control on no

TABLE 2

	Severe	Moderate	Mild
Hydrochlorothiazide	3	5	2
Hydrochlorothiazide plus Rauwolfia	1	2	
Guanethedine plus Rauwolfia	1		
Bendroflumethiazide (Naturetin) plus Rauwolfia	2	2	1
Rauwolfia	1		1
Bendroflumethiazide (Naturetin) plus hydralazine	2		
Guanethedine with hydrochlorothiazide	1		
No previous treatment	10	5	3
Chlorthalidone (Hygroton)		1	
Mebutamate (Capla)		1	
Hydralazine plus hydrochlorothiazide	1		
Rauwolfia plus nitrate compound		1	
Trichlormethiazide (Naqua) plus guanethedine	1		
Barbiturate			1

TABLE 3

Severity	Polythiazide Plus	Result
Severe	Hydralazine plus Guanethedine	Excellent
Severe	Guanethedine	Excellent
Severe	Guanethedine plus Hydralazine	Fair
Severe	Guanethedine plus Methyldopa	Excellent
Severe	Methyldopa	Excellent
Severe	Methyldopa	Excellent
Moderate	Rauwolfia	Excellent
Moderate	Guanethedine	Fair
Moderate	Guanethedine	Excellent

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*See Test Your Word Score Page 1573.

**Diabenese, Charles Pfizer and Company.

specific antihypertensive therapy for six weeks, the diastolic pressure then gradually rising to 100 mm. mercury.

The second diabetic patient was a 73-year-old white female, who was in left and right-sided cardiac failure when first seen. She had a mild blood pressure elevation, which fell 40 mm. systolic and 15 mm. diastolic with therapy. There was also a concomitant 35-pound weight loss. After 32 months a routine urinalysis showed glycosuria; blood sugar was 310 mg. per cent. Thiazides were discontinued, and she was easily controlled on small doses of chlorpropamide. She has remained out of failure and her blood pressure under control, for four months at the time of this report.

One patient was found to have diabetes and cardiac failure when first seen. He was easily controlled on chlorpropamide, while taking thiazides. A moderately elevated BUN. in one patient returned to normal on a decreased dosage, with no loss of blood pressure control.

Summary

A random group of 50 hypertensive patients have been most satisfactorily controlled and observed for one to three years with polythiazide as the sole hypotensive agent or as the cornerstone of therapy. Whether used as the sole hypotensive agent or in a multiple drug regime, in all but one case it was more effective than previous therapy. Eighty-six per cent of the patients showed excellent response to therapy; 14% showed fair response.

Fifty-six per cent of the group had elevated uric acids, with only two patients manifesting gouty symptoms. Precipitation of latent gout, diabetes, and hypokalemia are relatively common complications and should be sought assiduously in treatment with thiazides.

Commentary

A considerable number of these patients (24%), after blood pressure had been controlled for several months, could be maintained on significantly lower doses of thiazide. One patient has maintained a normal blood pressure for four months since polythiazide was discontinued.

One of the two patients dropped from the study group because of a dermatitis was resistant to multiple drug treatment; he was later controlled on a combination of polythiazide and Rauwolfia without side effects.

Acknowledgment

This work was supported in part by grants from the Minnesota Heart Association and Charles Pfizer and Company.

I am indebted to Mrs. Antonette Mestnick, Mrs. Angeline Johnson and Miss Sharon Sampson for their invaluable assistance.

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Derivatively Speaking

The juice formed by the liver may be called either bile or gall. *Bile* comes from the Latin word "bilis," which is what the Romans called the juice, but *gall* is Anglo-Saxon in origin. Both words are used in combination with others, and the choice of which to use depends on the derivation of the other word.

For instance, the juice is stored in a small pear-shaped bag called a *gall bladder* (never a "bile bladder," since *bladder*, like *gall*, is of Anglo-Saxon derivation), and is led into the intestines by means of a *bile duct* (never a "gall duct," since *duct* is from the Latin "ducere" meaning "to lead").

Hypocholesterolemia

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THOSE DISEASES and conditions associated with elevated serum cholesterol levels are well documented,[1] and it is to evaluate hypercholesterolemia that the serum cholesterol assay is most frequently performed. Less is known about hypocholesterolemia and its significance in disease. A study was undertaken to ascertain the diagnostic value of decreased serum cholesterol levels.

It is general knowledge that hyperthyroidism[2] and certain hepatic parenchymal disorders[3] are frequently associated with low serum cholesterol values. The diagnostic significance of lowered serum cholesterol in other disease states has been largely discounted. A detailed interpretation of hypocholesterolemia is advanced by Kolmer[4] in which 22 specific diseases are cited as a cause of, or associated with, decreased serum cholesterol. Several isolated articles have stressed the diagnostic significance of low cholesterol values in low fat ingestion,[5] rheumatic disease,[6] steatorrhea,[7] hypopituitary disease,[8] terminal stress,[9] anemia, infection,[6] pancreatitis,[10] and strenuous exercise.[11] In addition, various types of medication have been shown to depress serum cholesterol.[12]

Materials and Methods

Over 750 consecutive, low (less than 150 mg/100 ml.) cholesterol values were compiled, the determinations performed by the method of Abell. Values below 150 mg/100 ml. represented 3.4% of the total serum cholesterols assayed during the period of study. Approximately 90% of the specimens were drawn from hospital in-patients and the remainder from out-patients. Females accounted for 54% of the group. It is to be emphasized that this general hospital population was selected, since the presumptive diagnoses of these patients at the time the test was requested generally included hepatic diseases, thyroid diseases, and arteriosclerosis. Certain of the patients were diagnostic problems. The charts of all were studied and the diagnoses tabulated and analyzed. Only proven diagnoses were included in this final evaluation. Autopsies were performed on 3.3% of the population. Most of the patients had more than one diagnosed disease process.

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*Director, Clinical Laboratories, University of Utah.

To assist in evaluating *specific* cause and effect vs. *nonspecific* effect, the following empirical formula was used to "quantitate" any significant relationship that might exist between a given disease and the serum cholesterol level.

$$\frac{A \times B \times C \times D}{E} = \text{Factor of Relative Significance}$$

A = % of patients with some form of disease under consideration. This parameter is of obvious importance. In any determination, regardless of mechanism, specificity or frequency, if a given disease accounts for a high percentage of abnormal results, it must be given consideration in interpretation of results.

B = % of patients with some form of disease under consideration and no known additional concurrent disease process. If a patient has only one disease process and an abnormal test value, the probability is great that the abnormal result is related to the single disease process.

C = % of patients with some form of disease under consideration and at least one additional disease known to *elevate* serum cholesterol levels (biliary disease, myxedema, diabetes). It is logical to assume that any disease process occurring with a low-test value in a patient with a second disease known to "cause" high test values probably has considerable "cause-effect" significance.

D = approximate % of patients with some form of disease under consideration known to manifest hypocholesterolemia (for example 16% of patients with parenchymal disease of the liver have low serum cholesterol[10]). Obviously, if 90% of patients with a given disease had an abnormal test result, the degree of specifiicity and significance would be greater than if only 10% usually showed this abnormality. The figures used in this study were obtained, where possible, from the literature or estimated from hospital discharge statistics.

E = % of patients with some form of disease under consideration and at least one disease known to *depress* serum cholesterol (hyperthyroid disease, malabsorptive disorders, parenchymal disease of the liver). In the presence of a disease suspected of having an active effect on a given test value the similar effect of other diseases is open to question. Therefore the correlation is considered negative or reciprocal instead of cumulative, as with the foregoing situations.

Diseases showing frequency of less than 2.8% were not subjected to analysis since theoretically significant results would be invalid. The magnitude of cholesterol depression was not considdered in the formulation because no definite pattern of change was manifest. The mean cholesterol level for different diseases varied insignificantly from the total mean value.

Assuming that in a clinically well population 5% of the group would have cholesterols below 150 mg. per 100 ml. and conferring values of 1% to category C and E, a normal person with a low serum cholesterol would receive a Factor of Relative Significance of 125.

Results

On the basis of the results obtained from this formula, certain diseases or conditions apparently had an *active* cause or effect relationship on cholesterol levels, and other diseases apparently had a *passive* or incidental association. The figure 250 was considered the dividing line between significant and nonsignificant disease states. This figure was selected primarily because it was twice the value of the figure calculated for the theoretical normal person. These figures are tabulated in Table 1.

Of the incidental observations obtained in the study, the following deserve consideration.

1. The lower limit of normal usually quoted for serum cholesterols in American populations is probably too high for infants and for extremely elderly people, and too low for adults in the 20 to 60-year age group.[14] A more realistic lower limit of normal for this latter group would be 160 mg%. This conclusion is based on the fact that over 99.5% of the adult population in the study were clinically ill.

TABLE I
Tabulated Diagnoses of Low Cholesterol Levels in 750 Patients

Disease	% of Occurrence		Factor of Relative Significance
1. Parenchymal Liver Disease		38.5	10,873
2. Genitourinary Infections		27.0	2,565
3. Thyroid Disease		25.7	22,854
Toxic Goiter	17.2		
Nontoxic Goiter	3.3		
Thyroiditis	1.8		
Myxedema	3.5		
4. Heart Disease		14.0	173*
Hypertensive	2.4		
Arteriosclerotic	8.9		
Other	3.7		
5. Collagen Vascular Disease		11.9	30,151
6. Chronic Infections (except GU)		11.5	10*
7. Diabetes		11.1	36*
"Uncomplicated"	8.9		
Kimmelstiel-Wilson	2.2		
8. Malignancy, terminal		11.0	55*
9. Endocrine (Miscellaneous)		9.2	5,608
Hypopituitary	3.3		
Hypoadrenal	3.9		
Other	2.0		
10. Anemia (Primary)		6.6	3*
11. Chronic Gastrointestinal Dis.		6.3	65*
12. Chronic Pancreatic Disease		4.6	1,255
13. Exceptional Low-Fat Diets (ovo-lacto vegetarians, etc.)		2.8	406
14. Miscellaneous and Unknown (not subject to analysis)		14.7	*
Cortisone R_x	1.7		
Psychoneurosis	1.4		
Histocytosis	1.2		
Phlebothrombosis	1.2		
Dermatosis	1.2		
Demyelinating Disease	1.0		
Cushing's Syndrome	.9		
Mongolism	.9		
Polycythemia Vera	.7		
Cholelithiasis	.5		
Alopecia	.5		
Eclampsia	.4		
Muscular Dystrophy	.4		
Aortic Stenosis	.3		
Parathyroid Adenoma	.3		
Antihistamine R_x	.3		
Coarctation, aorta	.1		
Marfan's Syndrome	.1		
Hyperemesis Neonatorum	.1		
Endometriosis	.1		
Agammaglobulinemia	.1		
Sterility	.1		
Diagnosis undetermined (at time of study)	2.4		

*Not Significant.

2. Patients with genitourinary infections apparently have a higher incidence of hypocholesterolemia than patients with other types of infections. In many cases the genitourinary infection is either very mild or quiescent.

3. The incidence of hypocholesterolemia in diabetics was approximately four times higher in those patients with Kimmelstiel-Wilson involvement of their kidneys than in uncomplicated diabetics.

4. 11.9% of patients with low cholesterol had some form of collagen disease. Approximately twice this number of additional patients had certain symptoms and laboratory results that were best explained by collagen vascular disease, but did not have a proven diagnosis at the time of study. All auto-immune disorders were represented in this group.

5. All patients with hypocholesterolemia and myxedema had an associated collagen disease, hypopituitary disease, or recent thyroidectomy.

6. A patient with a rare oxyphil* adenoma of his parathyroid gland had an elevated cholesterol level prior to operation and a persistently decreased cholesterol after removal of the tumor.

7. Anemia, chronic infections, heart disease, terminal malignancy, chronic enteritis, diabetes and uremia were inactive in lowering serum cholesterol.

8. Free-ester cholesterol fraction rarely contributes useful information in hypocholesterolemic conditions. In all except two instances the free-esterified ratio was within normal limits. Both of these patients had abdominal malignancies which had massively infiltrated the mesenteric lymphatics.

Discussion

Factors detracting from the clinical significance attending serum cholesterol values are: variable technical results giving standard deviations of up to ± 10% ; wide variation of normal values relative to environment, general state of health, age, sex, inactivity, differences in technical methods, and dietary habits; and poor diagnostic correlation with disease processes. Many observers feel that assay of other serum lipid fractions contribute more useful information. Others point out that fluctuations are extremely nonspecific, and that the changes cited above are more frequently responsible for serum cholesterol variations than are the basic disease processes.

A compilation of lower limits of serum cholesterol defined by 15 investigators ranges from 97 to 190 mg/100 ml. These studies were performed on a total of 4313 "normal" American people of both sexes between the ages of 17 and 78 years of age. The mean cholesterol lower limit was 150.2 mg/100 ml. Several of these investigators indicated that their figures were based on division at the second standard deviation level. The lower limit of normal of the Abell procedure is 150 mg/100 ml. The standard variation of paired samples is within ± 5%.

It is difficult in this study to adequately evaluate the nonspecific effects of secondary starvation, prolonged bed rest, inactivity, and inanition on serum cholesterol level. Conclusive studies would involve complete dietary analysis, nitrogen balance studies, and serial lipid assays.**

The results of this study do not appreciably extend the diagnostic value of serum cholesterol determinations except for the apparent significant relationship of genitourinary infections and collagen vascular diseases to hypocholesterolemia. The negative contribution in instances of diabetes, chronic infections, heart disease, anemia, nonpancreatic gastrointestinal disease, and terminal disease including malignancy may have value in the implication and diagnosis of complicating disease processes.

Summary

A study was made of 750 patients with hypocholesterolemia. Thyroid hyperfunction, parenchymal disease of the liver, pancreatic insufficiency, profound low-fat diets, hypofunction of pituitary and adrenal glands, and collagen vascular diseases are the principal groups of diseases associated with active serum cholesterol reduction. Infections, anemia, terminal malignancy, heart disease, diabetes, and intestinal disorders appear to be only secondarily related to hypocholesterolemia.

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*See Test Your Word Score Page 1573.

**It is probable that these nonspecific factors would neutralize themselves by affecting all disease states equally.

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11-12. May be secured from the author or the reprints.

Desiderata*

Go placidly amid the noise and the haste, and remember what peace there may be in silence. As far as possible without surrender be on good terms with all persons. Speak your truth quietly and clearly; and listen to others, even the dull and ignorant; they too have their story. Avoid loud and aggressive persons, they are vexations to the spirit. If you compare yourself with others you may become vain and bitter; for always there will be greater and lesser persons than yourself. Enjoy your achievements as well as your plans. Keep interested in your own career, however humble; it is a real possession in the changing fortunes of time. Exercise caution in your business affairs; for the world is full of trickery. But let this not blind you to what virtue there is; many persons strive for high ideals; and everywhere life is full of heroism. Be yourself. Especially do not feign affection. Neither be cynical about love; for in the face of all aridity and disenchantment it is as perennial as the grass. Take kindly the counsel of the years, gracefully surrendering the things of youth. Nurture strength of spirit to shield you in sudden misfortune. But do not distress yourself with imaginings. Many fears are born of fatigue and loneliness. Beyond a wholesome discipline, be gentle with yourself. You are a child of the universe no less than the trees and the stars; you have a right to be here. And whether or not it is clear to you, no doubt the universe is unfolding as it should. Therefore be at peace with God, whatever you conceive Him to be, and whatever your labors and aspirations, in the noisy confusion of life keep peace with your soul. With all its sham, drudgery and broken dreams, it is still a beautiful world. Be careful. Strive to be happy.

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*Found in Old Saint Paul's Church, Baltimore, dated 1692.

ANSWER TO WHAT'S YOUR DIAGNOSIS

(From page 1550)

Abdominal exploration revealed a large tumor of the pancreatic head with two small metastases in the left hepatic lobe. Retroduodenal lymph nodes and the hepatic nodules showed adenocarcinoma. The gallbladder was distended and firm. There was no ascites.

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Dextro-amphetamine sulfate: Excessive use by unstable individuals may result in psychological dependence.

Meprobamate: Careful supervision of dose and amounts prescribed is advised, especially for patients with known propensity for taking excessive quantities of drugs. Excessive and prolonged use in susceptible persons, e.g. alcoholics, former addicts, and other severe psychoneurotics, has been reported to result in dependence on the drug. Where excessive dosage has continued for weeks or months, reduce dosage gradually. Sudden withdrawal may precipitate recurrence of preexisting symptoms such as anxiety, anorexia, or insomnia; or withdrawal reactions such as vomiting, ataxia, tremors, muscle twitching and, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, reduce dosage and avoid operation of motor vehicles, machinery or other activity requiring alertness. Effects of excessive alcohol consumption may be increased by meprobamate. Appropriate caution is recommended with patients prone to excessive drinking. In patients prone to both petit and grand mal epilepsy meprobamate may precipitate grand mal attacks. Prescribe cautiously and in small quantities to patients with suicidal tendencies.

Side Effects: Overstimulation of the central nervous system, jitteriness and insomnia or drowsiness.

Dextro-amphetamine sulfate: Insomnia, excitability, and increased motor activity are common and ordinarily mild side effects. Confusion, anxiety, aggressiveness, increased libido, and hallucinations have also been observed, especially in mentally ill patients. Rebound fatigue and depression may follow central stimulation. Other effects may include dry mouth, anorexia, nausea, vomiting, diarrhea, and increased cardiovascular reactivity.

Meprobamate: Drowsiness may occur and can be associated with ataxia; the symptom can usually be controlled by decreasing the dose, or by concomitant administration of central stimulants. Allergic or idiosyncratic reactions: maculopapular rash, acute nonthrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever, transient leukopenia. A case of fatal bullous dermatitis, following administration of meprobamate and prednisolone, has been reported. Hypersensitivity has produced fever, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, stomatitis, proctitis (1 case), anaphylaxis, agranulocytosis and thrombocytopenic purpura, and a fatal instance of aplastic anemia, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity, usually after excessive dosage. Impairment of visual accommodation. Massive overdosage may produce drowsiness lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

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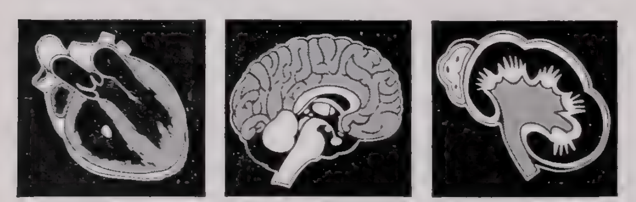
SQUIBB NOTES ON THERAPY

Behind continued high blood pressure readings lies the possibility of organic damage[1-13]

MANY OF THE aspects of essential hypertension are unpredictable—either because there are a number of mechanisms involved or because individuals differ in their responses to these mechanisms.[1]

There is one aspect of hypertension, however, that seems, in many cases, predictable. ". . . when the blood pressure is elevated to a marked degree for an adequate period of time, this in itself leads to perpetuation of the syndrome with resulting vascular damage throughout the body."[14] All too often the disease progresses until there is damage to one of three vital organs: the heart, the kidney, the brain.



> "Hypertension is certainly a major factor in the genesis of coronary heart disease, and it is even more important when compounded with obesity."[4]
>
> "[Vascular deterioration] can be clearly seen in the kidney with a degree of damage that can be measured by renal function studies."[10]

". . . most evidence suggests that reduction of blood pressure, when it is too high, not only relieves the heart of excess work but reduces vascular damage."[1]

"In short, treatment is indicated."[1]

Antihypertensive therapy will not restore the blood vessels to normal. Yet many of the vascular changes and symptoms caused by increased blood pressure may be arrested or alleviated when the blood pressure is reduced to normotensive levels.[7]

Reducing the blood pressure helps curtail further vascular damage and improves the prognosis — when damage is not too far advanced before therapy is started.[14] Essential hypertension is an indication not only for treatment, but for *early* and adequate treatment of the patient in question.

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Rautrax-N combines the antihypertensive-tranquilizing action of whole root rauwolfia with the antihypertensive-diuretic action of bendroflumethiazide in one convenient medication. The two drugs complement each other so that smaller doses of both are possible.

Rauwolfia combined with bendroflumethiazide is particularly effective in long-term therapy,[15-17] since beneficial effects do not diminish with continuous daily administration.

For most patients 1 or 2 Rautrax-N tablets daily are sufficient for maintenance therapy. The simplicity, convenience and economy of such a dosage schedule are of particular benefit to older patients.

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Contraindications: Severe renal impairment or previous hypersensitivity. **Warning:** Ulcerative small bowel lesions have occurred with potassium-containing thiazide preparations or with enteric-coated potassium salts supplementally. Stop medication if abdominal pain, distension, nausea, vomiting or G.I. bleeding occur.

Precautions and Side Effects: The dose of ganglionic blocking agents, veratrum or hydralazine when used concomitantly must be reduced by at least 50% to avoid orthostatic hypotension. Caution is indicated in patients with depression, suicidal tendencies, peptic ulcer; electrolyte disturbances are possible in cirrhotic or digitalized patients. Marked hypotension during surgery is possible; consider discontinuing two weeks prior to elective surgery and observe patients closely during emergency surgery. Rauwolfia preparations may cause reversible extrapyramidal symptoms and emotional depression, diarrhea, weight gain, edema, drowsiness may occur. Bendroflumethiazide may cause increases in serum uric acid, unmask diabetes, increase glycemia and glycosuria in diabetic patients, and may cause hypochloremic alkalosis, hypokalemia; cramps, pruritus, paresthesias, rashes may occur.

Dosage and Supply: Initial dosage, 1 to 4 tablets daily, preferably at mealtime. Maintenance, 1 or 2 tablets daily. Rautrax-N is supplied as capsule-shaped tablets containing 50 mg. Rauwolfia serpentina whole root (Raudixin®), 4 mg. bendroflumethiazide (Naturetin®), 400 mg. potassium chloride.

Also available: Rautrax-N Modified — capsule-shaped tablets containing 50 mg. Rauwolfia serpentina whole root (Raudixin), 2 mg. bendroflumethiazide (Naturetin), 400 mg. potassium chloride. Both potencies available in bottles of 100. For full information, see Product Brief.

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Editorials

Meniere's Disease*

ENDOLYMPHATIC HYDROPS, or hypertension of the labyrinth, remains a great unsolved problem in the practice of otology. The causes of this condition are obscure and treatment by medical means has been as variable as the theories proposed for an explanation of the increased endolymphatic pressure.

Symptomatic improvement can be expected in most cases with judicious medical treatment and psychotherapy, or by spontaneous remission. The occasional severe case which has failed to respond to medical management and presents a persistence or recurrence of disabling vertigo with severe hearing loss requires surgical intervention.

One feature of this condition, which is more commonly referred to as Meniere's disease, has been definitely established. This is the gross distention of the endolymphatic system, along with degenerative changes in the Organ of Corti. The relationship between increased endolymphatic pressure and the typical hearing loss of Meniere's disease has also been clarified and established. Experiments have demonstrated that increasing the endolymphatic pressure in animals by injection of a hypertonic solution into the scala media results in a decrease of cochlear potentials and a return to normal upon release of the pressure.

Intractable vertigo with severe permanent hearing loss resulting from Meniere's disease has been treated surgically by various procedures employing a direct attack on the labyrinth for the purpose of destroying the endolymphatic system and indirectly affecting also the cochlea resulting in hearing loss. Neurosurgical section of the eighth cranial nerve has been replaced by the safer methods of opening the horizontal semicircular canal or the oval window within the middle ear, by transtemporal bone approach, to extract the endolymphatic labyrinth. These procedures have been used only in cases which have precluded a profound hearing loss with a disabling vertigo. Where useful hearing is still present, and especially when both ears are involved with hydrops of the labyrinth, it becomes desirable and hopeful to attempt relief of vertigo without destroying the residual hearing function.

Ultra-sound applied to the bony horizontal semicircular canal has been used and can affect relief of vertigo, but the result may not be permanent and in many cases facial paralysis has resulted. An approach through the stapes footplate to reach the labyrinth and relieve pressure of endolymph

Continued

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*See Surgical Treatment of Dizziness Page 1531.

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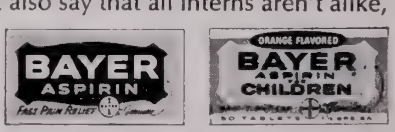
You might also say that all interns aren't alike, either.



by penetration of the dilated saccule with a perforating hook has been used. With this technique, however, as in other procedures using a direct attack on the labyrinth, a large percentage of cases result in increased hearing loss.

Drainage of the saccus endolymphaticus has been described for some time as the logical type of treatment of Meniere's disease. The difficulties encountered in many procedures designed for drainage of endolymph are related to accurate identification of the saccus and subsequent fibrotic growth hindering continued escape of endolymph. It has become evident that simple drainage of endolymph affords only temporary relief of vertigo and that the longer drainage can be maintained, the longer the patient will be free of symptoms.

Experiments now indicate that the buildup of excessive endolymphatic pressure as a cause of Meniere's disease is probably due to a faulty absorption mechanism rather than an acute pathologic process in the endolymphatic system. Creation of a permanent fistula to aid or correct this disturbed fluid balance seems therefore to be a sound and more effective physiologic approach to the problem of maintaining permanent relief of endolymphatic pressure.

Conrad J. Holmberg, M.D.
Minneapolis, Minnesota

Anti—Nuclear Antibodies in Various Diseases*

THE SIGNIFICANCE of the numerous antinuclear factors which have been discovered in the serum in various diseases is still not clear after almost two decades of investigation. These antibodies were initially found in the course of studies on the nature of the lupus erythematosus (LE) factor which subsequently was discovered to be γ-globulin. A number of antibodies have since been identified, which react with deoxyribonucleoprotein (DNP), deoxyribonucleic acid (DNA), a glycoprotein extracted from whole nuclei by isotonic neutral buffers, nucleoli (possibly RNA), histone (the protein moiety of DNP), and microsomes and mitochondria, the antigenic parts of which have not yet been determined. Of these, only anti-DNA has been found to be specific. It is present only in patients with disseminated lupus erythematosus, and the amount present varies directly with the severity and acuteness of the disease. Its presence can be detected by complement fixation, by immune precipitation, by a fluorescent-spot technique, or by a characteristic "shaggy" pattern of the nuclei of leukocytes coated with this antibody and then developed with fluorescent anti-human γ-globulin.

The most commonly found antibody is anti-DNP, the antibody probably studied by Gokcen, Peterson, and Ehrnst.* This antibody is present in a wide variety of inflammatory disorders and in diseases characterized by tissue necrosis. The finding of such reactivity in patients with tumors, as reported by these authors, suggests that when the test is set at a very sensitive level this reactivity is diagnostically not much more helpful than any other acute-phase reactant. Its presence does not necessarily imply that any auto-immune reaction is causing the patient's symptoms.

In fact, it is very unlikely that anti-nuclear antibodies themselves cause any direct harmful effects on cell nuclei, as they do not cross the cell membrane of living cells. Anti-nuclear antibodies may react with dead or degenerated nuclear material and thus induce migration of polymorphonuclear leukocytes and an ensuing inflammatory response, but there is no good evidence at present that such a mechanism is actually important in any known human disease. The relationship of anti-DNP to the LE-cell-forming factor has not been worked out in detail; the LE factor does seem to be an anti-DNP antibody. Whether the fact that not all patients with anti-DNP give positive LE clot tests is due to quantitative differences in the

Continued

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*Gokcen, Muharrem et al.: Anti-Nuclear Antibodies in Various Disease. Minnesota Med 49:920, 1966.

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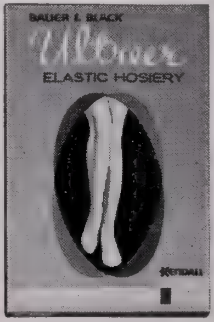

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amount of antibody present or to other factors is not known. Not all patients with positive LE clot tests have detectable anti-DNP in their sera.

The high incidence (50%) of positive anti-nuclear tests in rheumatic fever in the series reported is also probably explained by the high sensitivity and low specificity of the test used. The authors stated that they are now titrating their sera, and the use of a semiquantitative test may improve the diagnostic usefulness of their method. However, since they did not examine any of the patients themselves but merely used the diagnoses on charts called from several hospitals and representing the opinions of a large number of physicians, it is impossible to have much confidence in the significance of their results.

Frederic C. McDuffie, M.D.
Rochester, Minnesota

Macroglobulins, Microglobulins, and the New Terminology

THE ARTICLE by Bell and Neumann* reporting some studies on characterization of the macroglobulins found in a group of eight patients provides a vehicle enabling us to make a plea for rapid transition to the new terminology for immunoglobulins.[1] Massive increases in macroglobulins such as those found in Waldenström's macroglobulinemias, or in microglobulins — so called L-chains or Bence-Jones proteins (associated with multiple myeloma) — are actually exaggerations of normal constituents of the serum protein spectrum. The immunoglobulins — so-called because their primary function in body economy seems to be to carry or provide antibody specificity — have been called as many different names as some of our early 20th century political parties. Public awareness of their importance was apparent as long as a decade ago when, as Dr. Waldenström observed during a visit to Boston, angry mothers were picketing with signs announcing "We Want Gamma Globulin!". His first reaction, he told us, was "What a progressive country!".

The new nomenclature for the immunoglobulins has been proposed by the Bulletin of the World Health Organization and is quite simple. The old terms 7-S γ-globulin, gamma-2 globulins, γSS, γ-globulin (all meaning the same thing to the initiated fraternity of workers in this field) have been simplified to γG or IgG (immunoglobulin G). γG comprises 75-80% of the bulk of antibody molecules in human serum. The second major immunoglobulin class (old terms — gamma$_1$A, B$_2$A, β_2A) now goes by the simpler term γA or IgA. This second immunoglobulin class (10-15% of immunoglobulins) seems to be associated in many instances with skin reactivity and may be of special significance in conferring an unique immune system to the gastrointestinal tract. The third major immunoglobulin class (old terms — gamma$_1$M, macroglobulins, 19S-γ-globulins, heavy antibody) is now called γM or IgM. All three major groups of immunoglobulins IgG, IgA, and IgM are comprised of heavy (H) and light (L) polypeptide chains linked by disulfide bonds. Antigenic cross reactions occur among these three major immunoglobulin classes on the light chains which are identical to the microglobulins or Bence-Jones proteins often excreted in the urines of patients with multiple myeloma.

When sera such as those reported in the accompanying article by Bell and Neumann are matched with the clinical picture of the individual patients, it has been our general experience that many of the subjects studied fall into the general broad category of malignant lymphoma. This view is also borne out by the recent study of Krauss and Sokal.[2] In terms of the laboratory diagnosis of Waldenström's macroglobulinemia by far the quickest and most reliable technique is immunoelectrophoresis combined with quantitative assay of IgM using Oudin tube techniques[3] or analytical ultracentri-

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*See Minnesota Med 49:753, 1966.

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fugation. The Sia or water dilution test which depends on the formation of an insoluble euglobulin in distilled water has too often proved negative in the face of macroglobulinemia well documented by the above mentioned specific immunologic methods.

Ralph C. Williams, M.D.
Minneapolis, Minnesota

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The Incompetent Cervix*

THE INCOMPETENT cervix is now a recognized entity responsible for second-trimester cervical effacement and dilatation, resulting in pregnancy loss due to low fetal salvage if untreated. The success of surgical procedures to correct the incompetent cervix and prevent second-trimester fetal loss associated with this condition is undeniable. Surgery has been employed on the external cervical os, midcervical region, or the internal cervical os as well as on all three simultaneously, with reports of success rates of 50 to 95%. Surgical correction has been advocated during pregnancy as a therapeutic measure and during the nonpregnant state as a prophylactic measure against recurrence in future pregnancies. Cerclage** can be accomplished at either time. Surgical reconstruction of the cervix is performed on the nonpregnant uterus.

Cerclage, during pregnancy, seems to be gaining in acceptance as the method of choice, although individual preferences exist.

The cause of cervical incompetence often is not clear. Structural changes, secondary to cervical trauma, may be a factor in some cases; or the structure of the cervix may be congenitally abnormal, resulting in primary cervical incompetence. Where no structural defect is apparent, some physicians believe that a physiologic or dysfunctional type of cervical incompetence, based on anatomic or hormonal relationships, exists. In some cases the cervix may be normal by all known criteria; yet a grossly abnormal cervix often maintains a pregnancy without difficulty. Herein exists a threat to accurate selection of patients for treatment, resulting in differences of reported incidence and cures. Unfortunately, definitive diagnosis of cervical incompetence often escapes accurate measurement in the nonpregnant uterus. Cervical-balloon studies, catheter-traction techniques, examination with Hegar dilators, and cervicohysterography have been employed with variable reports of success, but all methods leave something to be desired in demonstrating cervical incompetence. During pregnancy the diagnosis is more objective and is determined by the observation of progressive, painless, cervical effacement and dilatation. Symptomatology contributes little; however, a history of previous midtrimester pregnancy loss should alert the physician to the possibility of cervical incompetence. Diagnosis during pregnancy requires immediate treatment, preferably surgical. Various transvaginal surgical techniques to effect closure of the cervix may be used, or a purse-string type of constriction may be produced at the internal os level by cerclage with fascia, silk, Merseline, Teflon, or other polyester fiber strips. Treatment can also be accomplished transabdominally if the cervix does not seem suitable for transvaginal techniques. Preference for vaginal or abdominal delivery varies, although most surgeons select abdominal delivery. If nonabsorbable material is used for cerclage, this must be cut or removed prior to vaginal de-

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*Stromme, W. B., Wagner, R. M., and Haywa, E. W.: The Incompetent Cervix. Minnesota Med 49:393, 1966.

**See Test Your Word Score Page 1573.

BE A MYTH-MONGER #3

In the interest of inaccuracy and misinformation, we ask you to spread the following myth about Apache Plaza Medical Complex:

APACHE PLAZA MEDICAL COMPLEX IS ON THE NORTHEAST EDGE OF MINNEAPOLIS. EVERYBODY KNOWS THAT PEOPLE IN THAT AREA ARE POOR CREDIT RISKS.

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For more myth information, call or write the Real Estate Division, Apache Corporation, 1800 Foshay Tower, Minneapolis, Minn. 55402. Telephone: (612) 339-7781.

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BE A MYTH-MONGER #4

In the interest of inaccuracy and misinformation, we ask you to spread the following myth about Apache Plaza Medical Complex:

DOCTORS!! APACHE PLAZA'S MEDICAL COMPLEX DOES NOT HAVE A HOSPITAL NEXT TO IT.

True enough, it doesn't. The closest hospitals to Apache Plaza Medical Complex are from 9 to 15 minutes away. But then again, we must remember . . . over 95 per cent of a doctor's patients do not require hospitalization. By relocating adjacent to a hospital, you might put a geographic imposition on your patients, as well as your previous hospital commitments.
Doctor . . . as a matter of fact, Apache Plaza is the center of the community for all of northwest St. Paul, northeast Minneapolis, and suburbs.

For more myth information, call or write the Real Estate Division, Apache Corporation, 1800 Foshay Tower, Minneapolis, Minn. 55402. Telephone: (612) 339-7781.

APACHE PLAZA MEDICAL COMPLEX

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livery. Rupture of the uterus has been reported when labor occurred and this was not done. A few patients have been successfully treated by prolonged rest in bed, beginning about the sixteenth week of pregnancy. This is almost impossible outside of the hospital, and the cost is formidable to the patient, with little hope of achieving a successful outcome. Endocrine therapy seems to be of little or no value in treatment.

True cervical incompetence is a relatively rare condition, occurring in 1:300 to 1:600 obstetric cases. A large obstetric service is needed to collect an appreciable number of patients if strict diagnostic criteria are observed. Surgery on patients with only a history of first trimester fetal loss is ill advised. From the standpoint of prevention, cautious and minimal dilatation of the cervix during curettage is recommended, and avoidance of rapid fetal extraction or difficult forceps delivery would seem indicated.

Carl E. Johnson, M.D.
Rochester, Minnesota

Auto-Immune Hemolytic Anemia

AUTO-IMMUNE HEMOLYTIC anemia (AIHA) appears to be an indisputable violation of Ehrlich's dictum of "horror autotoxicus." Yunis and Bridges in their article appearing in the May issue* have cited evidence that clearly shows many patients with the warm antibody type of AIHA have antibodies with Rh-Hr specificity. Detailed serologic studies often show these antibodies to react with blood group antigens inherited by the patient under study. Another group of patients with AIHA, the cold antibody type, generally have a favorable prognosis. Their antibodies show specificity for the i-antigen, a blood-group determinant found on their erythrocytes and the erythrocytes of most humans.

Leddy and Bakemier[1] have studied the structural characteristics of IγG globulins eluted from the erythrocytes of patients with the warm antibody type AIHA. Twelve of twenty patients showed monotypic reactions and eight bytypic reactions when tested with type K and L antisera. The occurrence of Coombs-positive** hemolytic anemia associated with thymic lesions in NZB mice has provided an experimental model to study other aspects of AIHA.

Other observations have cast more than reasonable doubt on the auto-immune etiology of this anemia. Zuelzer[2] has isolated cytomegalic virus from children with warm antibody type AIHA. Anti-i has been found in the serum of patients with infectious mononucleosis in cases with and without hemolytic anemia. Hillman and Giblett[3] have shown a change in the amount of i-antigen on the red cell that seems to be related to a decreased bone-marrow maturation time, and it has been shown that the i-antigen content of erythrocytes can be altered after incubation with mycoplasma species.

Whether AIHA is a disease of autoimmune origin or is secondary to some infectious agent will perhaps be answered with time. The practical problems of therapy for these patients, however, must be faced now. Steroids, immunosuppressive drugs, splenectomy, and even thymectomy have their advocates. Regardless of the basic therapeutic modality employed, both the pathologist and the clinician are presented with a dilemma when transfusions are considered to alleviate the anemia in patients with AIHA. The former, as pointed out by Yunis and Bridges, must make a negative choice, i.e., the least incompatible blood; the latter must contend with a less than expected response, or even a deterioration of the patient after transfusion.

To aid the pathologist in his search for the least incompatible blood, the clinician must allow adequate time for a thorough serologic investigation. In-vivo compatibility tests with Cr^{51}-labelled red cells may help in this quest. In some instances, plasmapheresis and autotransfusion may be the answer to the compatibility problem. A reduction in the patient's blood volume and an increase in his

Continued

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*Minnesota Med 49:759, 1966.

**See page 1596.

Winthrop announces new

WinGel®

ANTACID TABLETS AND LIQUID

For peptic ulcer, gastric hyperacidity, gastritis

Each WinGel tablet or teaspoon (5 ml.) contains 410 mg. of combined, highly reactive, short polymer, aluminum and magnesium hydroxides **stabilized with hexitol.**

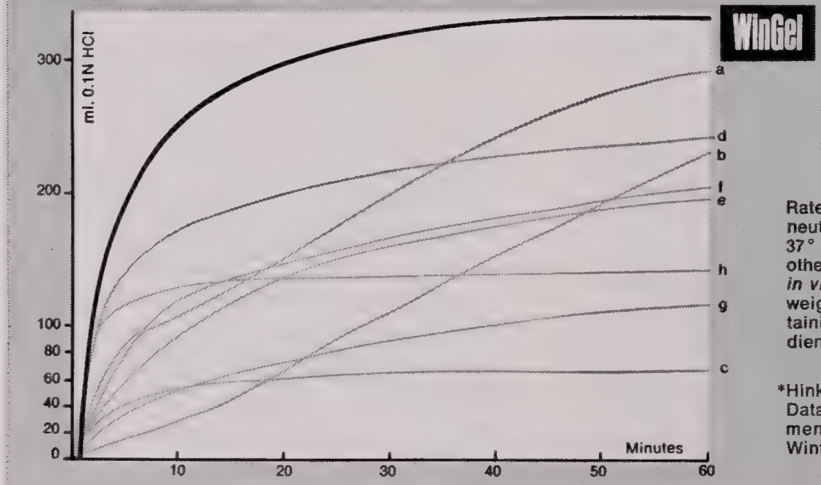
Neutralizes 300 times its active-ingredient weight in gastric acid for fast, long-lasting relief

Gastric or duodenal ulcer, acute or chronic gastritis, gastric hyperacidity...wherever there is "acid overflow" new WinGel can provide faster, longer, more complete neutralization.

In recent laboratory comparisons* with eight other leading antacids, new WinGel tablets not only neutralized more hydrochloric acid per active-ingredient weight, but neutralized it faster and longer than all other antacids tested.

Pleasant pink in color, WinGel is delicately mint flavored with a smooth-as-cream texture—qualities sure to please the patient on long-term therapy. New WinGel is also specially formulated to avoid constipation or diarrhea.

New WinGel neutralizes 300 times its active-ingredient weight in 0.1N hydrochloric acid—neutralizes more acid faster than other leading antacids



Rate of 0.1N hydrochloric acid neutralization at pH 3.5 and 37° with WinGel and eight other leading antacid tablets—*in vitro*. Samples equaled the weight of tablet material containing 1.0 Gm. active ingredients.*

*Hinkel, E. T., Jr. (New York): Data in the files of the Department of Medical Research, Winthrop Laboratories.

Dosage: Peptic ulcer or gastritis—from 2 to 4 teaspoons of WinGel liquid or 2 to 4 tablets chewed or allowed to dissolve in the mouth every two to four hours. **Gastric hyperacidity**—2 tablets or teaspoons about ½ to one hour after meals as needed; children from 7 to 14 years of age, 1 or 2 tablets or 1 or 2 teaspoons of liquid as needed.

How Supplied: Liquid in bottles of 8 fl. oz. and 1 pint. **Tablets** in cellophane strips, boxes of 50 and 100. (One teaspoon of WinGel liquid is equivalent to one WinGel tablet in acid-combining capacity.) WinGel, trademark reg. U.S. Pat. Off.

Winthrop Laboratories, New York, N.Y. 10016 Winthrop

Finally — a taste your patients will truly like

(1058M)

red-cell volume without the risk of sensitization to additional red-cell antigens can be accomplished.

In some cases, in spite of bed rest, supportive therapy, etc., heart failure and/or anoxia may make transfusion imperative. In these individuals packed red cells are the therapy of choice. These should be administered cautiously and the patient carefully observed during and following the transfusions for a possible reaction.

Herbert F. Polesky, M.D.
Minneapolis, Minnesota

References

1. Leddy, J. P., and Bakemier, R. F.: J Exp Med 121:1, 1965.
2. Zuelzer, W. W.: Emily Cooley Lecture Presented at the 18th Annual Meeting of the American Association of Blood Banks, Bal Harbour, Florida, 1965.
3. Hillman, R. S., and Giblett, E. R.: J Clin Invest 44:1730, 1965.

Test Your Word Score

Nomogram — *three graduated lines with two of known value from which the third can be determined* (page 1524).

Episodic—*occurring as separate events* (page 1531).

Potpourri—*a mixture, as of spiced flower petals in a jar, used to scent a room* (page 1535).

Apocrine glands—*glands in which cells contribute substance to secretion* (page 1539).

Anacrotic—*abbreviation for anadichrotic, twice beating on the upstroke* (page 1547).

Maculopapular—*a papule rising from a macule* (page 1553).

Oxyphil—*acid-staining cells* (page 1558).

Cerclage—*binding together of the ends of a fracture bone by a metal ring or wire loop* (page 1569).

Gobbledegook n.—*(Coined by Maury Maverick of Texas, as representing sounds made by the stupid and pompous turkey cock.) Inflated, involved, and obscure verbiage such as is often found in the pronouncements of officialdom* (Page 1581).

Leukoencephalopathy—*genetical cerebral disorder affecting myelin* (page 1630).

Hyperkinesia—*excessive mobility* (page 1590).

In courtship a man pursues a woman until she catches him.

To help dispel the symptoms
of mild depressive states

CONSIDER **DEXAMYL®** FIRST
brand of dextroamphetamine sulfate and amobarbital

Often within the hour, 'Dexamyl' works to help dispel such symptoms as apathy, pessimism, loss of interest and initiative, and lack of ability to concentrate.

Formulas: Each 'Dexamyl' Spansule® capsule (brand of sustained release capsule) No. 1 contains 10 mg. of Dexedrine® (brand of dextroamphetamine sulfate) and 1 gr. of amobarbital, derivative of barbituric acid [Warning, may be habit forming]. Each 'Dexamyl' *Spansule* capsule No. 2 contains 15 mg. of Dexedrine (brand of dextroamphetamine sulfate) and 1½ gr. of amobarbital [Warning, may be habit forming].

The following is a brief precautionary statement. Before prescribing, the physician should be familiar with the complete prescribing information in SK&F literature or *PDR*.

Precautions: Use with caution in patients hypersensitive to sympathomimetics or barbiturates and in coronary or cardiovascular disease or severe hypertension. Do not use in patients taking MAO inhibitors. Excessive use of the amphetamines by unstable individuals may result in a psychological dependence; in these instances, withdraw the medication. Use cautiously in pregnant patients, especially in the first trimester. *Side effects:* Insomnia, excitability and increased motor activity are infrequent and ordinarily mild.

SK&F SMITH KLINE & FRENCH LABORATORIES

You May Be Right

The concluding statement in my editorial regarding The Scimitar Syndrome should have been as follows.

"A more painstaking search of the literature to include for example the paper entitled The Scimitar Syndrome by Sanger et al, Archives of Surgery, Volume 86, page 84, 1963; a report of five cases undergoing surgery would have further embellished the report of this surgical achievement."

Joseph J. Garamella, M.D.
Minneapolis, Minnesota

I Thought the Government Was Fighting Rebates

I have recently read for the first time that some of the drug houses are giving special prices, or rebates, to hospitals for Medicare and welfare patients. If drug houses can reduce their prices in this way, must they not be charging too much in the first place, and possibly could they not reduce prices of all drugs? The individual who pays his way may in some instances have limited resources, and such individuals are probably more deserving of lower prices than those who are being cared for by the government.

It has been indicated that this benefit can apply to any of the 19,000,000 persons over age 65 who are eligible for Part A of Medicare. Robert J. Meyers, Chief Actuary of the Social Security Administration, has estimated that if all drug companies were to make the same 25% reimbursement the government could save perhaps 3 to 4 percent of Medicare hospital costs. Is it possible that the government is interested in saving 3 or 4 percent on anything?

Perhaps there are others who have some feeling about this rebate from many of the reputable pharmacal laboratories.

Harry B. Neel, M.D.
Albert Lea, Minnesota

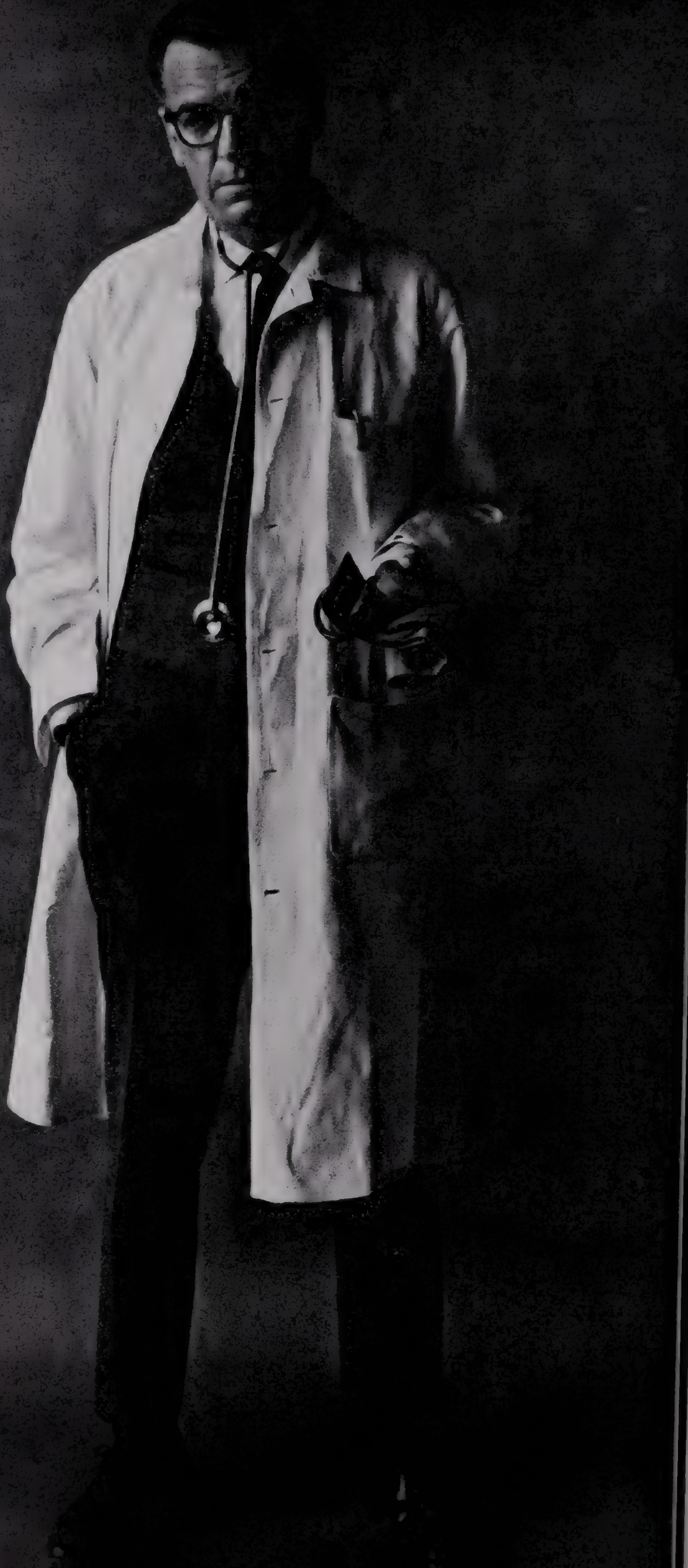
Dietitians, Education, and the Future

Dietitians are full partners in the business of taking care of diabetic patients and might well be partners in the other fields of medicine. As we finish our schooling and take stock of the situations available to us, we find that our vocation presents a much greater variety of opportunities than we had anticipated.

In the field of dietetics this may include among other things work in institutions, commercial food-processing concerns, public health, and nutritional research, as well as in the usual field of hospital dietetics. Each of these varieties of work requires different talents, and these talents are not measured necessarily by our grades in school. In institutional work an ability for organization and management may determine one's success,

Continued

Frankly, most antihypertensives are pretty good if you give an adequate dose. I'm looking for one with a simple regimen so that mix-ups in doses and therefore the chance of side effects are minimized.



Regroton®

chlorthalidone 50 mg. reserpine 0.25 mg.

1 tablet daily brings pressure down

Advantage: Both components of Regroton are long-acting.
Average dosage: One tablet daily with breakfast.
Contraindications: History of mental depression, hypersensitivity, and most cases of severe renal or hepatic diseases.
Warning: Discontinue 2 weeks before general anesthesia, 1 week before electroshock therapy, and if depression or peptic ulcer occurs. With administration of enteric-coated potassium supplements, the possibility of small bowel lesions should be kept in mind.
Precautions: Reduce dosage of concomitant antihypertensive agents by one-half. Discontinue if the BUN rises or liver dysfunction is aggravated. Electrolyte imbalance and potassium depletion may occur; take particular care in cirrhosis or severe ischemic heart disease and in patients receiving corticosteroids, ACTH, or digitalis. Salt restriction is not recommended. Use with caution in patients with ulcerative colitis, gallstones, or bronchial asthma.
Side effects: Nausea, vomiting, diarrhea, muscle cramps, headaches and dizziness. Potential side effects include angina pectoris, anxiety, depression, drowsiness, hyperglycemia, hyperuricemia, lassitude, leukopenia, nasal stuffiness, nightmare, purpura, urticaria, and weakness.
For full details, see the complete prescribing information.
Availability: Bottles of 100 and 1000 tablets.

Geigy

but such an ability probably did not help in getting a good grade in biochemistry. Warmth of personality is not measured by grades in mathematics or psychology.

As the field of dietetics and nutrition advances, the individual dietitian will need to keep abreast of developments or gradually become obsolescent.

One may say that the obvious answer to the problem is the assiduous reading of several professional journals and regular attendance at the annual meetings of the professional societies. Such measures surely are desirable and necessary, but they may not be adequate. The answer proposed for this dilemma is continuing education. Such studying cannot be done by casually picking up bits of information from journals. It necessitates an organized, methodical review of the subject. If we do not develop and apply programs of continuing education, we will face the penalty of obsolescence, an occupational junkyard.

A good preparation in mathematics, chemistry, and physiology during one's undergraduate years gives one the best chance for staying abreast of technical advances.

Perhaps the most challenging medical problem we have today is atherosclerosis, and there is much to suggest that it is primarily a complex nutritional problem with additional factors of hereditary susceptibility and exercises. In certain diseases such as peptic ulcer and diabetes, in which dietary therapy is primary, many of our dietary rules for these diseases are impairing and have little factual basis. Some diseases are not ordinarily thought of as nutritional, but the optimal treatment for them may require new dietetic approaches. Examples of these might be hyperthyroidism and collagen diseases. Our changing industrial environment, with the chance of accumulation of traces of various elements or toxic organic substances, may permit emergence of yet unrecognized syndromes with nutritional components.

Finding sources of protein for an over-populated world is a problem. Protein can be derived from mass-processed whole fish or leaves, but the political, economic, and dietetic problems of utilizing such sources have not yet been solved. The physician, the biochemist, and the physiologist will be concerned about nutritional problems, and the person who leads the way may carry any of these labels and will need the cooperation of someone in each of the other fields. The dietitian, if she is qualified, may well find herself playing an increasingly important role. In order to provide dietitians for the future we will need to recruit undergraduate students with first-rate abilities in chemistry, mathematics, and the physiologic sciences. We will not be able to describe the particulars of her future job. We can be sure, however, that it will be challenging.

Clifford F. Gastineau, M.D.
Rochester, Minnesota

Freedom without obligation is anarchy; freedom with obligation is democracy. —
Earl Riney

SQUIBB NOTES ON THERAPY

Breast-feeding and the "modern mother"

Despite a mild resurgence of interest in the importance of breast-feeding a few years ago, many women today do not choose to nurse their young. This is for a variety of reasons—social, economic, cultural and sometimes medical. In such cases the physician's task is to find the most suitable means of preventing lactation and easing the pain of breast engorgement.

The means of therapy

The value of hormone therapy for this indication is of course well established. Both androgen and estrogen are known to inhibit the production and secretion of the lactogenic hormone by the anterior pituitary. As estrogen levels decline sharply at parturition, lactogenesis is established. When androgen and estrogen are administered to the patient before the release of the lactogenic hormone lactation and breast engorgement are usually prevented.

The time of therapy

The time of administration of this combined medication is crucial; it must be given early enough to suppress the pituitary prolactin and last long enough to permit physiologic readjustment during the puerperium. Excellent results are most often seen when therapy is administered before the onset of the second stage of labor.

However, factors other than effectiveness must also be considered. The agent selected should not interfere in any way with parturition, subsequent uterine involution and the restoration of normal ovarian cyclic function. Furthermore, it should not cause rebound breast engorgement or other manifestations of hormonal imbalance.

A balanced formulation

Providing single-dose therapy for the prevention of lactation and breast engorgement, Deladumone OB is a potent androgen-estrogen combination with a prolonged action. The optimal balance of androgenic and estrogenic hormones achieved in this preparation minimizes the disadvantages inherent in single hormone therapy, such as rebound breast engorgement. Involution of the uterus and resumption of menstrual cycles are not affected.

As reported in a recent published study (Roser, D. M.: Obstet. & Gynec. *27*:73, 1966), Deladumone OB provided good suppression of breast engorgement in 95.3% and suppression of lactation in 81.1% of 86 obstetrical patients. These results are in general agreement with those of many earlier investigations; in several studies this injectable androgen-estrogen combination proved to be superior to oral medication.

Dosage:

As a single injection of 2 cc. before the onset of the second stage of labor.

Contraindications:

Established or suspected mammary cancer or genital malignancy.

Precautions and Side Effects:

Certain patients may be unusually responsive to either estrogenic or androgenic therapy. In such individuals virilization, uterine bleeding or mastodynia may occur.

Supply:

Deladumone OB, providing 180 mg. testosterone enanthate and 8 mg. estradiol valerate per cc., is available in 2 cc. Unimatic® disposable syringes and in 2 cc. vials. Both preparations are dissolved in sesame oil, with 2% benzyl alcohol as a preservative. *Before use, consult product literature for full prescribing information.*

Deladumone® OB

Squibb Testosterone Enanthate (180 mg./cc.)
and Estradiol Valerate (8 mg./cc.)
Single-dose injection for lactation inhibition

SQUIBB *'The Priceless Ingredient' of every product is the honor and integrity of its maker.*

The Ailing Pioneer
His Ague

"Don't go to Michigan, that land of ills;
The word means ague, fever and chills."

Although the miseries that plagued the Midwest pioneer could hardly match the tribulations of a Job, they were indeed considerable. Whereas Job had boils, the pioneer had the ague. In fact, ague was so common that it was hardly regarded as a disease — but rather as an endemic feature of frontier life.

Its etiology was never definitely determined: most of the natives blamed the fickle climate and the miasmatic soil, cavalierly ignoring deficient diet and lack of sanitation. Historian James Hall, however, claimed that excessive consumption of meat and alcohol was responsible for the ague; the Medical Repository commented: "The inhabitants are almost constantly in a state of repletion, by stuffing and cramming, and by the use of stimulating drink;"* and Dr. Daniel Drake went so far as to point out the danger of spontaneous combustion in the human body from the ingestion of too much animal fat and spirituous liquor: "As a general fact, the people of the Valley (Mississippi) eat too much. The bodies of corpulent inebriates, when asleep, have, in several instances, taken fire, by the accidental contact of a burning coal or candle, and all the soft parts have been reduced to ashes, or driven off in clouds of thick smoke. To conceive of the possibility of this revolting catastrophe, we need only recollect the combustible nature of fat, and the still more inflammable quality of ardent spirits."*

Nomenclature-minded physicians classified the types of ague. Dr. William Daily's categories included Continued, Remitting, and Intermitting — with the paroxysms differentiated into Quotidian (morning-occurring), Tertian (noon-occurring), and Quartan (afternoon-occurring) not to mention such further confounding reductions as Simple and Double, Anticipated and Postponed.

Ague victims shook! Sometimes so hard as to rattle the dishes on the shelves! One family shivered so violently in unison that workmen shingling their roof were frightened off by the vibration. Babies were born quaking! Even the cattle were not immune but shuddered so vehemently that they had to lean against the fences for support.

For a vicarious fit of the ague the imaginative reader has only to peruse a partial description by one articulate victim:

"You felt as though you had gone through some sort of collision, thrashing-machine or jarring-machine, and came out not killed, but next thing to it. You felt weak, as though you had run too far after something, and then didn't catch it. Your back was out of fix, your head ached and your appetite crazy. Your eyes had too much white in them, your ears had too much roar in them, and your whole body and soul were entirely woebegone. You didn't think too much of yourself and didn't believe that other people did, either; and you didn't care. About this time, if you had the strength and means, you picked up Hannah and the baby, and your traps, and went back 'yander' to 'Old Virginny,' the 'Jerseys,' Maryland or 'Pennsylvany.' "*

A few pioneers did return whence they had come. But the hardiest stayed on.

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*Pickard and Buley: The Midwest Pioneer. Henry Schuman, New York, 1946.

when agitation

accompanies

spasm of the

'G. I.' tract.

Butadonna

BUTABARBITAL SODIUM 15 MG. [illegible]
[illegible] MAY BE HABIT FORMING
BELLADONNA EXTRACT [illegible]

provides gentle,

intermediate sedation and

relaxes 'G. I.' spasm.

Butadonna quiets the "brain-on-gut" influences by providing the smooth, intermediate sedative, butabarbital sodium, desirable in combination with the proven antispasmodic, belladonna extract. Butabarbital sodium is more rapidly eliminated than phenobarbital, and avoids the latter's cumulative effect.

Indications: Antispasmodic-sedative. Useful in the treatment of peptic ulcer, gastritis, duodenitis, irritable colon syndrome, ulcerative colitis, regional enteritis, and other conditions associated with gastrointestinal spasm. Also may be useful in functional dysmenorrhea.

Usual adult dosage is one tablet 3 or 4 times daily as needed.

Caution: Contraindicated in glaucoma and urinary retention. Reduce dosage or discontinue use in event of blurring of vision, dryness of mouth, tachycardia, or excessive drowsiness. Continued use of butabarbital sodium may be habit forming.

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The Editor's Soliloquy

Gobbledegook* at the Meeting

Your editor took notes at the annual convention of the Society for the Ancillary Obligations Correlating the Conduct of the Incorrigible but Nevertheless Deserving where it appeared that: the medical specialties detailing the modalities of the allied species integrating — their responsibility to the general concept were represented by the respective members. — Moreover, the qualifications and scientific liabilities relating to the respective care available to each and everyone demonstrates the vast need for — a close liaison for discharging and terminating the obligation and correlating the conduct for the protection of the intellectual public.

"No element of the Committee for Reliable Judgment — a subsection of the main body of the AA — dealing with the logistics of the paramedical parameters and its relative obligatory discipline — essential to the enlightened methodology have been given adequate implementation.

"Another categorical must in the propitious perspective of our great and glorious tradition — a society for the operational promotion and exploitation of attitudes pursuant to and congruent with our hypothetical aims so — eloquently enunciated and unanimously sanctioned for the prevention of catastrophic contingencies — as well as for the quantitative formalization and content-analysis of policies for the preservation of stability within the context of experience. Supplemented by an auxiliary commission — for the recruiting and mobilizing of the total corpus of our honorable members in their endorsement and corroboration of agitation and propaganda to finalize the same.

"I realize that I have posed more problems than I have solved and presented more challenges than I can meet, but not without imagination and dedication to the security of a noble profession so fervently engaged in the promulgation and proliferation of its shining ideals of service and the promotion of its heroic crusade within a dynamic framework of ancillary reference."

Believe it or not: that is what your bemused editor heard!

Carl O. Rice, M.D.

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*See Test Your Word Score Page 1573.

Mom says: That wolf! He looks very sexsusful.

(1) Have something to say; (2) Say it; (3) Stop as soon as you have said it; (4) Give the paper a proper title.

John Shaw Billings, M.D.
source not known

after surgery

B and C vitamins are therapy: Therapeutic amounts of B and C in stress formula vitamins often are vital during periods of physiologic stress. STRESSCAPS capsules, designed to meet increased metabolic demands, aid in achieving a more comfortable convalescence, a more rapid recovery. After surgery, as in many stress conditions, STRESSCAPS vitamins are therapy.

Stresscaps®
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FOR PROFESSIONAL
RECOMMENDATION ONLY

Each capsule contains:

Vitamin B_1 (Thiamine Mononitrate)	10 mg
Vitamin B_2 (Riboflavin)	10 mg
Vitamin B_6 (Pyridoxine HCl)	2 mg
Vitamin B_{12} Crystalline	4 mcgm
Vitamin C (Ascorbic Acid)	300 mg
Niacinamide	100 mg
Calcium Pantothenate	20 mg

Recommended intake: Adults, 1 capsule daily, for the treatment of vitamin deficiencies. Supplied in decorative "reminder" jars of 30 and 100; bottles of 500.

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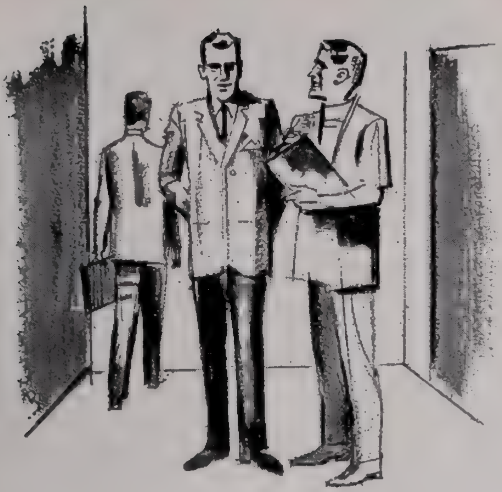

Curbstone Consultation

Pulmonary Function Test

QUESTION: What is the best method of doing a pulmonary function test in the doctor's office without employing expensive equipment?

ANSWER: Vital capacity can be determined with a simple spyrometer or other available device. Though it is usually reduced during attacks, and especially when interim asthma continues, a normal or higher value does not rule out emphysema even of the destructive type.

When vital capacity returns to normal with relief from bronchial asthma, resulting from the control of inhalant and especially of food allergy, irreversible obstructive emphysema has not occurred.

A more accepted office test is the first second volume of forced expiration below 45% of the vital capacity. Franklin and Lowell favor determination of the E 50-75, which is the expiratory flow rate in the 3rd quarter of forced expiration, expressed in cc./second. Abnormal values are below 1300 cc. in patients over 40 years of age. In severe, obstructive emphysema the values often are between 300 and 700 cc.

When bronchial asthma, associated with reversible emphysema is relieved by control of inhalant and especially of chronic food allergy, these tests return to normal. When destructive emphysema has occurred, especially when an allergic or asthmatic predisposition is present, improvement in these tests may be slight or absent.

The good or excellent relief in symptoms in such destructive emphysema, usually with chronic bronchitis, which we reported at the meeting of the A.M.A. in June resulted from the control of inhalants and especially of food allergy, was not associated with corresponding improvement in these tests. This indicates that the benefit was due to the relief of bronchospasm, edema in the airways, and bronchorrhea arising from chronic allergy and not from a reduction in the destructive changes in the lungs. This relief continues with or without minimal oral or inhalant bronchodilators and corticoid therapy, providing the allergy, especially to foods, is rigidly controlled. These results challenge every physician to study and control food, and to a lesser extent inhalant allergy in all these cases with emphysema.

Albert H. Rowe, M.D.
Oakland, California

When offered a penny for their thoughts, few people are honest enough to admit they can't make change. — Mundy Smith

SQUIBB NOTES ON THERAPY

MOLECULAR REMODELING–

laboratory exercise or clinical necessity?

More than twenty-five years have passed since the discovery of the diuretic activity of sulfanilamide started pharmacologists on a succession of molecular remodelings to find the ideal diuretic.

Diuresis–a sought-after clinical effect from an unwanted side effect

It started in 1937 when a clinician reported that the administration of a sulfonamide was sometimes accompanied by an unexplainable side effect–metabolic acidosis.[1] Three years later the side effect was explained. The sulfonamide radical of sulfanilamide inhibited carbonic anhydrase,[2] the enzyme responsible for converting carbon dioxide and water to hydrogen ions and bicarbonate ions.

Later, other investigators showed by dog experiments that metabolic acidosis probably resulted when the inhibition of carbonic anhydrase upset the exchange of hydrogen and sodium ions, causing increased excretion of sodium as the bicarbonate.[3]

It was twelve long years after the first report of the unexplainable side effect (metabolic acidosis) that it was finally shown that large doses of sulfanilamide administered to edematous patients were indeed capable of promoting diuresis.[4] However, the possibility of toxic effects from its prolonged use and its relatively weak diuretic action made it impractical for clinical use as a diuretic.[5]

Because the inhibition of carbonic anhydrase seemed to be the key to effective diuresis, investigators began to look for more potent enzyme inhibitors —in the hopes that they would be more effective diuretics.

The most important of these early compounds, acetazolamide, enjoyed several years of fairly wide clinical use.

Its carbonic anhydrase inhibitory activity was several hundred times greater than that of sulfanilamide.[6] The increase in inhibitory activity, however, increased not only the excretion of sodium and bicarbonate ions, but also the excretion of potassium.[7] And, like its predecessor, acetazolamide precipitated mild acidosis. Its prolonged use could result in hypokalemic acidosis.[7]

The 'thiazides'–an answer to the metabolic acidosis caused by carbonic anhydrase inhibition

Despite the fact that the sulfonamide group appeared to be responsible for carbonic anhydrase inhibition which in turn appeared to be responsible for diuresis, investigators began to synthesize compounds with structural alterations to the sulfonamide group.

The first major breakthrough came with the synthesis of chlorothiazide. Altering the sulfonamide group did indeed alter the ability of chlorothiazide to inhibit carbonic anhydrase–it was only 1/10th as potent as acetazolamide in inhibiting the enzyme.[8] Despite the drop in inhibitory potency, however, chlorothiazide proved to be an effective diuretic–an observation that led to the conclusion that its diuretic action was due to some mechanism other than its action on carbonic anhydrase.[9, 10]

For effective diuresis, chlorothiazide was administered in daily dosages ranging from 250 to 2000 mg.[11] It increased the excretion of sodium and chloride; and, to a lesser extent, potassium and bicarbonate.[11] The excretion of potassium appeared to be maximal at higher dose levels at which, theoretically, the carbonic anhydrase inhibitory effect is more active.[11] Its prolonged use, therefore, could sometimes result in metabolic hypokalemic, hypochloremic alkalosis.[7]

Naturetin–effective diuresis with more favorable electrolyte balance

Other thiazides followed—with improvements being aimed at two particular areas: 1. attempts to increase diuretic action in relation to the milligram potency of the drug, and 2. attempts at a more favorable sodium/potassium ratio in the urine, i.e., to decrease the excretion of potassium while maintaining the excretion of sodium.[12]

One of these, Naturetin, Squibb Bendroflumethiazide, has made advances on both these points. "By adding a 3-benzyl radical to hydroflumethiazide a rather dramatic reduction in dose range is accomplished. With this drug, effective sodium excretion is obtained with doses between 2.5 and 10 mg., which is a 200 to 1 ratio as compared to chlorothiazide..."[13]

Moreover, due probably to its virtual lack of carbonic anhydrase inhibition, Naturetin (bendroflumethiazide) has been shown to cause less potassium and bicarbonate loss and less alteration in urinary pH than either chlorothiazide or hydrochlorothiazide.

Naturetin is outstandingly effective not only in establishing, but also in maintaining, excretion of retained fluid in edematous patients. And its duration of action is sufficiently prolonged to allow a single daily administration in most patients. Naturetin is also an effective antihypertensive agent.

Contraindications: Severe renal impairment; previous hypersensitivity.

Warning: Ulcerative small bowel lesions have occurred with potassium-containing thiazide preparations or with enteric-coated potassium salts supplementally. Stop medication if abdominal pain, distension, nausea, vomiting, or G.I. bleeding occur.

Precautions: The dosage of ganglionic blocking agents, veratrum, or hydralazine when used concomitantly must be reduced by at least 50% to avoid orthostatic hypotension. Electrolyte disturbances are possible in cirrhotic or digitalized patients.

Side Effects: Bendroflumethiazide may cause increases in serum uric acid, unmask diabetes, increase glycemia and glycosuria in diabetic patients and may cause hypochloremic alkalosis, hypokalemia; cramps, pruritus, paresthesias, and rashes may occur.

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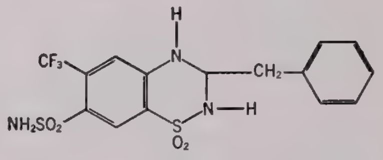
References: **1.** Southworth, H.: Proc. Soc. Exper. Biol. & Med. *36*:58, 1937. **2.** Mann, T. and Keilin, D.: Nature *146*:164, 1940. **3.** Pitts, R. F., and Alexander, R. S.: Am. J. Physiol. *144*:239, 1945. **4.** Schwartz, W. B.: New England J. Med. *240*:173, 1949. **5.** Friedberg, C. K., in Moyer, J. H., and Fuchs, M.: Edema Mechanisms and Management, Philadelphia, W. B. Saunders Co., 1960, p. 259. **6.** Cumming, J. R.; Tabachnick, E., and Seelig, M., in Moyer, J. H., and Fuchs, M.: op. cit., p. 254. **7.** Werko, L., in Moyer, J. H., and Fuchs, M.: op. cit., p. 188. **8.** Beyer, K. H., Jr., in Moyer, J. H., and Fuchs, M.: op. cit., p. 274. **9.** Maren, T. H., and Wiley, C. E.: J. Pharmacol. & Exper. Therap. *143*:230, 1964. **10.** Earley, L. E., and Orloff, J.: Ann. Rev. Med. *15*:149, 1964. **11.** Fuchs, M., and Mallin, S. R., in Moyer, J. H., and Fuchs, M.: op. cit., p. 276. **12.** Ford, R. V., in Moyer, J. H., and Fuchs, M.: op. cit., p. 290. **13.** cited in Fuchs, M., and Mallin, S. R. (ref. 11): op. cit., p. 283.



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The Viewing Box

Metastatic Carcinoma to the Brain

A 60-YEAR-OLD white male was admitted to the University of Minnesota Hospitals with a chief complaint of severe right frontal and retro-orbital headaches of five weeks' duration. He had also noted intermittent blurring of vision and dizziness. Significant past history included a partial bladder resection two years earlier for carcinoma.

Physical examination revealed an emaciated individual with a slight left-sided hemiparesis. Reflexes were normal and symmetrical. Examination of the eyegrounds showed a minimal degree of papilledema. There was no evident visual field cut.

A right carotid angiogram was performed.

Roentgenographic Findings

The plain film examination of the skull was normal. The pineal gland was not calcified.

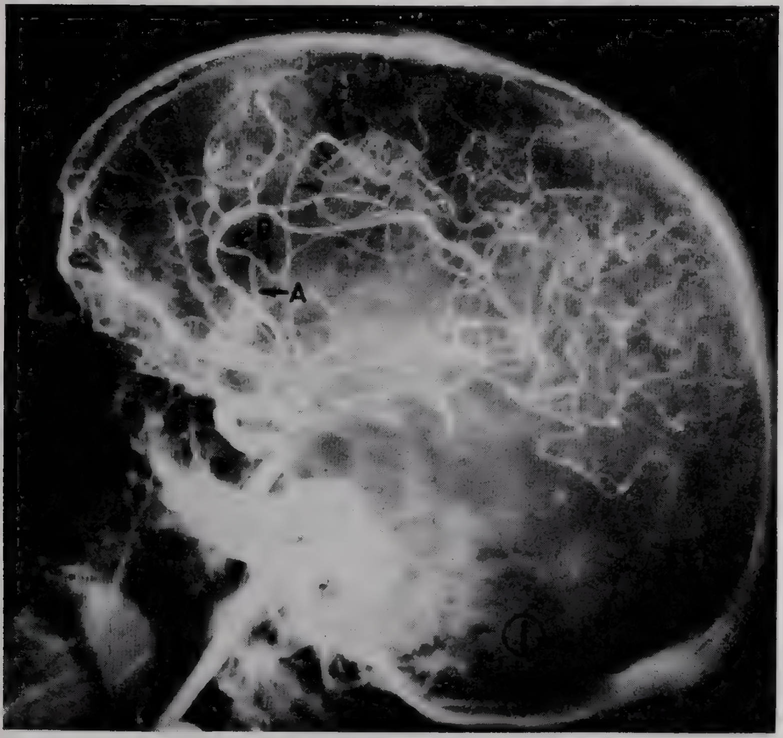

Figure 1

The initial film of the right carotid angiogram (Figure 1), made in the arterial phase of circulation, shows depression of the branches of the middle cerebral artery in the anterior portion of the Sylvian fissure. The ascending frontoparietal branch of the middle cerebral artery (labelled "A") divides into two main branches ("B"), each of which proceeds upward over the convexity of the frontal lobe and then ("C") gives off a number of terminal branches in an abnormal configuration (unlabelled arrows).

Continued

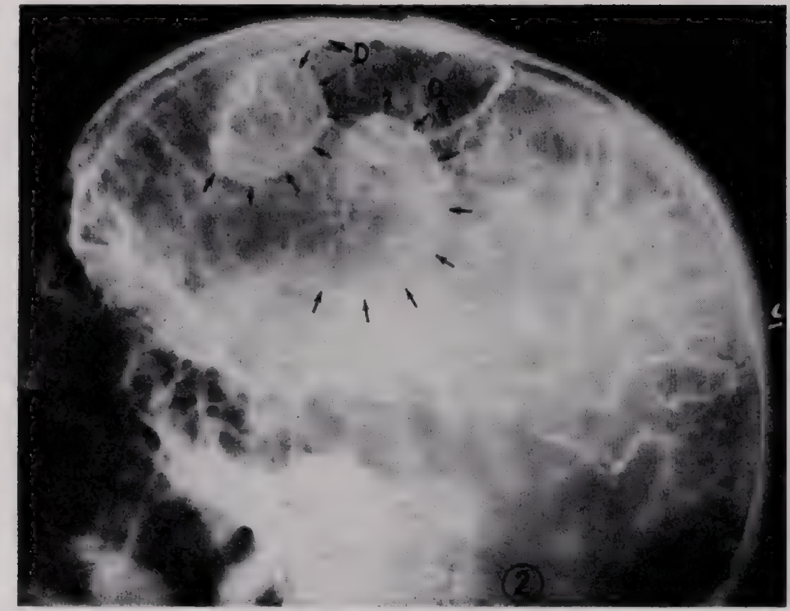

Figure 2

A film made later in the arterial phase (Figure 2) shows two well defined vascular masses (unlabelled arrows) in the same areas as the terminal branches described in Figure 1. The tiny vessels clustered mainly on the periphery of these masses drain into large veins ("D") which flow upward over the convexity of the frontal lobe to drain into the superior sagittal sinus. Note that the remainder of the brain is still in the arterial phase, emphasizing the rapid circulation of contrast medium through these masses.

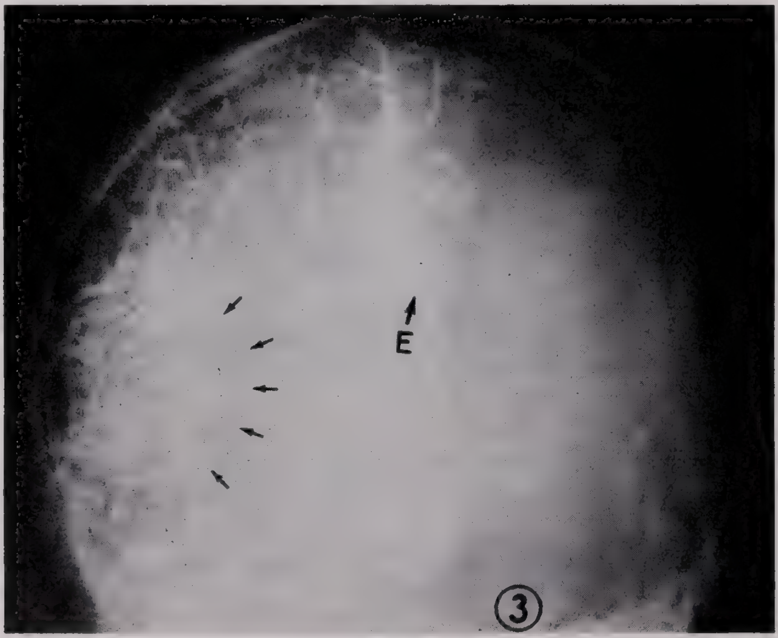

Figure 3

Figure 3, an anteroposterior projection, shows displacement of the anterior cerebral artery to the left of the midline. When the branches of this artery reach the falx, they abruptly return to the midline ("E"). The larger of the two vascular masses is outlined on its medial aspect by the line of unlabelled arrows.

DIAGNOSIS: METASTATIC CARCINOMA TO THE BRAIN.

Comment

About five per cent of all patients dying with malignant disease have cerebral metastases. These tumors comprise about twenty per cent of all neoplasms of the brain.[1] At time of diagnosis, either by angiography or at necropsy, they are usually multiple, although about thirty per cent of cases in reported series had only solitary metastases in the brain.

Small metastases are usually found near the junction of the cortex and the white matter of the brain, a point in common with emboli in general. This is likely due to the sudden transition from the vascular gray to the relatively avascular white matter. Since metastasis to the brain is commonly accepted to be via the arterial route, this abrupt transition in size and number of vessels would provide a logical stopping point for blood-borne emboli of tumor cells.

The most common source of cerebral metastases is the lung. Over one half of the patients in the large series reported by Russell and Rubinstein[1] and by Chason, Walker, and Landers[2] had their primary carcinoma in the lung. One rationale for this predominance is that these tumors, by invading and seeding into the pulmonary venous system, can bypass the filter of the lung, through which blood-borne cells from other tumors must pass before reaching the brain. Other fairly common sources of cerebral metastases include breast, kidney, and melanoma. The latter tumor, though rarer by far than cancer of the lung, kidney, or breast, shows a remarkable predilection to metastasize to the brain. A primary in the bladder, as in this case, is relatively rare.

The diagnosis of cerebral metastasis by angiography is not always an easy one.[3,4] Multiplicity of lesions, as in this patient, is perhaps the best sign. Metastases generally are well defined rounded masses with peripheral vascularity, usually situated in the terminal region of a given artery. They are often surrounded by extensive edema. Circulation through these usually highly vascular tumors is rapid with early venous filling, as seen above. The differentiation from a vascular astrocytoma or glioblastoma on the basis of angiography may be difficult, emphasizing the importance of demonstrating multiple tumors.

Treatment of these patients is generally palliative and usually includes the administration of systemic corticoids to reduce the accompanying cerebral edema.[5] Surgical removal of solitary lesions or external radiation therapy of the cerebrum in patients with angiographically demonstrated multiple lesions may be of some benefit.

Stephen A. Kieffer, M.D.*
Harold O. Peterson, M.D.
Minneapolis, Minnesota

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*Scholar in Radiological Research of the James Picker Foundation Department of Radiology, University of Minnesota Hospitals.

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3-5 May be secured from the reprints or the author.

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Neuro-Pediatrics Conference

*Hyperactivity, Behavior Problems**

Minimal Organic Cerebral Dysfunction or Environmental Deficit?

THIS EIGHT-YEAR-OLD girl was first seen at the University Hospital on June 18, 1965, at the request of Dr. J. Havel because of school adjustment problems.

Dr. Ted Buselmeier**

Although the initial visit was precipitated by hyperactivity and lack of attentiveness in school it was soon apparent the patient has been somewhat of a problem at home since late infancy. The mother says the child has always been somewhat nervous, has had difficulty getting along with her sibs, and has difficulty forming friendship relationships with other children her age. She has been on Hydroxyzine hydrochloride (Atarax) 1-10 mg. tablet four times daily since early fall. The mother has noted no improvement with this treatment until the last two to three weeks coincident with a change to two tablets twice daily.

The child had frequent "colds," skin eruptions (apparently associated with ingestion of tomato), and uncomplicated measles at 3½ years. If not awakened she also wets the bed once during the night. Past history is otherwise unremarkable.

Examination revealed a pleasant but apprehensive blond girl with no significant physical deficits. She responded to some questions with an anxious "I forgot." Neurological examination revealed poor hand coordination, poor left-right discrimination, and number and letter reversal.

Many eosinophiles were noted on nasal smear; urinalysis revealed 1 plus albumin on one occasion (culture negative), and an electroencephalogram was interpreted as mildly abnormal because of some diffuse and localized slowing in the left mid and posterior temporal area.

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*Sponsored by the U. S. Public Health Service Grant N2502A63. These conferences are an integral part of the Comprehensive Clinic Program at the University of Minnesota Hospitals. The pediatric conferences are held weekly from 1 to 2 p.m. every Wednesday. The adult conferences are held every Thursday at 4 p.m. Co-ordinators for the project are Dr. Edward C. Defoe and Dr. Charles Branthaver in Pediatrics and Dr. Robert Soll in Adult Neurology.

**Student physician, University of Minnesota Hospitals.

Continued

Dr. Bernard Lemieux*

I had the opportunity of seeing this child only once. Her head circumference was 57 cm., which is normal for a child of this weight and height. Her cranial nerves were intact and gross motor examination was normal with regard to strength and tonus. She is right-handed; however, when asked she is unable to discriminate between right and left. (Ability to so discriminate is usually developed at the age of six years.) As might be expected with a right-handed person, she was less well coordinated on the left than the right. Some choreiform movements of the fingers (particularly on the right) were demonstrable with the arms outstretched. Finger discrimination was performed less well on the left than on the right. Less use of the left arm was noted with running.

Moderate bilateral synkinesis or mirror movements were observed, which may have a developmental origin, if bilateral, or may be a manifestation of mild pyramidal hemisyndrome, if unilateral.

The history of immediate postnatal complications manifested by cyanotic spells and minor seizures and the above subtle neurological findings left me with an impression that she has a static minimal cerebral dysfunction of "organic nature manifest by a hyperkinetic behavior."

The minimal neurological findings may also be developmental in nature, which might be confirmed in a subsequent examination. A Bender or a WISC test often helps to substantiate this clinical impression.

A recent report notes abnormal slow wave frequencies as being the most consistent electroencephalographic changes in association with hyperkinesis in children. However, this tracing which showed mild diffuse and localized slowing in the left mid-posterior temporal area does not correlate well with the left-sided physical findings. All we can say about this particular electroencephalogram being specific is that the pattern is consistent with that which may be seen in hyperkinetic children of organic origin.

Dr. Edward Defoe**

What points do you use for differentiating a hyperkinetic syndrome secondary to minimal organic brain damage from the clinically similar one which relates primarily to a decrease in environmental input?

Dr. Lemieux

We perform all of the standard neurological tests including assessment of walking and running gait, fine coordination, recognition, etc. Usually the functionally hyperactive children perform well for their mental age. The child with organic disease is somewhat more clumsy, does not demonstrate bilateral coordination proficiency to the degree that he should, does not use one arm as much as usual with running, or has mild pyramidal findings. Environmental factors may be superimposed and, if so, act as uninhibited incoming sensory stimuli distressing the disorganized and immature brain, thereby contributing to the earlier appearance and the amplification of the hyperkinesis.

The hyperkinetic syndrome† should be considered under at least four different possible origins: developmental, environmental, psychiatric, and finally organic (see minimal cerebral dysfunction). Seen alone or in combination, those etiologies should as far as possible be dissociated, and no single cause should be disregarded to the detriment of any other.

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*Pediatric Neurologist, University of Minnesota Hospitals.

**Conference Moderator, University of Minnesota Hospitals.

†See Test Your Word Score Page 1573.

Dr. Defoe

It is important for us to recognize that hyperkinesis is found in children with no evidence for organic dysfunction. It is equally important to recognize that the hyperkinesis found in the child with evidence for organic cerebral dysfunction is often only indirectly related. We have a tendency to treat initially with drugs and ignore other factors in the presence of definable organic disease. Yet it is obvious that the child with cognitive and coordination difficulties is the one in whom environmental input may be less than optimal. Careful investigation of environmental factors which may be etiologically significant is indicated regardless of the presence or absence of history or subtle neurological variation suggestive of organic disease.

Dr. Robert Havel*

The mother's pregnancy was uneventful. (However, she did have some problems with fatigue and with "blacking-out and fainting spells" for a time after the pregnancy.) Delivery was uneventful after an intravenous pitocin induction.

Difficulty with respiration and several spells of cyanosis and hypertonicity for the baby in the neonatal period were attributed (by a pediatric consultant) to airway obstruction from excess mucus. Following discharge from the hospital the infant did reasonably well. When seen at six weeks her weight was 9 lbs. 5 oz. and she was reported to be somewhat fussy. She was not seen again until 10 months of age, at which time she weighed 20 lbs. 4 oz. and was having no difficulty.

Aside from several brief visits for minor complaints the child was not seen again until March 1965, because of the school difficulties, nervousness and hyperactivity. At that time we found nothing remarkable on physical examination. Examination by an ophthalmologist was also unremarkable. An electroencephalogram was reported as unsatisfactory because of hyperactivity.

Mrs. Helen Tressel**

From the beginning this child was considered by her kindergarten teacher to be strange and difficult to understand. I think the children also thought she was a little odd. She had a difficult time in the first grade, particularly with other children, with whom she fought a good deal. In the second grade we were able to do a little more and at this time we noted she had difficulty getting words straight. When we tried using different colors for a word, she made some improvement. She was quite difficult to manage and to keep contented. She liked to roam and investigate. However, she did learn to read somewhat and doesn't appear significantly below class-room intelligence level. Miss Moore now has her in the third grade.

Miss Shirley Moore†

Although she seems to enjoy reading, her performance is below the

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*Referring Physician.
**Principal, Standish Elementary School.
†Teacher, Standish Elementary School.

Continued

average in the group. She has considerable difficulty with arithmetic and demands my help even to the point of crying out across the room, "You have to help me." She does not seek help from other children. She works pretty well by herself when she knows what to do. If she fails to understand things she just falls apart. She is easily hurt by the other children and will cry and come to the teacher for reassurance and approval. However, she has improved a good deal since the beginning of the year. I understand the mother has changed the medication; this may be a big factor. Perhaps she knows that I accept her the way she is and that the children also accept her; so she may not be so frustrated.

Dr. Harold Ireton*

What do you think are the specific reasons for this change? How have you handled troublesome situations such as her hollering across the room?

Miss Moore

The children in the room pay little attention to this now. She receives a minimum of attention for negative behavior.

Mrs. Tressel

Last year she received a good deal of attention for negative behavior (fighting with another girl in the class). However, this year the two have been separated. I believe the grouping of the children this year has made a difference.

Miss Eleanor Brandtner**

I have observed change and improvement which seems to be due to understanding by the mother and to the fact that the teacher is not threatened by what she does. She is more relaxed not only because of the medication but also because of the feeling of security.

Dr. Defoe

I suspect you have put your finger on the real reason for improvement. Actually, as far as drugs are concerned, she has not had an increase in dosage but rather a change in time of administration. In addition there is little objective evidence that this particular drug (Hydroxyzine hydrochloride-Atarax) is useful in the treatment of hyperkinetic states. I do not believe we can attribute improvement to a change in the medication.

Mrs. Carolyn Mowery†

We have had an interrupted, unsteady kind of contact with this family since April, 1965. The mother who is in her eighth month of pregnancy has missed several visits because of illness and for other reasons. The father seems to have lost interest in coming, due in part at least to his father's illness and a peculiar dependent relationship which appears to exist between the patient's father and paternal grandfather. There are also problems with the fourteen-year-old and the ten-year-old boys. The teacher has pointed out that the latter is making "animal noises" to the extent that they are quite disturbing to the school. I am also impressed with the inconsistency of the parents' management of the chil-

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*Clinical Psychologist, University of Minnesota Hospitals.
**Social Worker, Standish Elementary School.
†Social Worker, Lutheran Welfare Agency.

dren. The mother is certainly a nervous type of person, primarily involved in the discipline responsibility.

Miss Maxine Boyd*

Although she enjoys coming and has no trouble sitting for an hour or so, this child has trouble sticking with things that are difficult for her. Anxiety and anger tend to make her forget. She has obvious need for gratification. She eats a good deal and always notices when anyone has candy or food. Although she doesn't ask directly she constantly tries to create situations which will permit her to participate directly in food consumption.

Mrs. Rachel Watt**

The oldest boy in the family is 15 years old and in the tenth grade. He was somewhat upset when the family moved to their present address three years ago.

The other boy is ten years old and in the fifth grade. The patient is eight years old and in the third grade. The youngest child is now two years old, and the mother is expecting the birth of their fifth child about December 17, 1965. The parents plan to stay permanently in their present home. It has four bedrooms, three up, one down; a living room, dining room, kitchen and full basement. Their financial situation is understandably tight. The mother would like to stay in the hospital longer than three days when the baby is born, but her husband has only three days vacation and there is no money to engage full or part-time help. They are preparing the older boys to be of as much help as possible.

The patient apparently is getting along well in her present neighborhood. There are plenty of children to play with, and the mother does not feel she has to be constantly supervising, as the child is now more reliable and obeys regulations as to play areas, crossing the street, etc. She still has some odd behavior activities, however, such as emptying all the ice-cube trays into an end table drawer and "wasping" up toilet paper into big balls. The mother is irritated by this; but the father gives the impression of almost tactile identification with his daughter's enjoyment in this.

Impression:

These parents have been coping in a rather blind and limited fashion with child-rearing responsibilities. Married when very young, they still have many unsatisfied ego needs, and both appear to be somewhat anxious and apprehensive. Added to this are the financial pressures and a fifth child expected about December 17. Both parents have responded well to family counseling at Lutheran Welfare and are able to use suggestions and guidelines effectively. This family is continuing with Lutheran Social Service and expressed much relief and satisfaction with the casework service they are receiving there.

Dr. Harold Ireton

Current and past psychological evaluations yield the picture of a child with reasonably average intellectual ability (verbal-abstract skills) but

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*Social Worker, Lutheran Welfare Agency.
**Social Worker, University of Minnesota Hospitals.

Continued

with significant perceptual and perceptual-motor problems. Intelligence testing in March, 1965, with the Wechsler Intelligence Scale for children indicated a verbal I.Q. of 92, but with a performance I.Q. of only 83. This below-average performance I.Q. is consistent with her performance on other largely non-verbal tests, where she is somewhat inferior for her age. This pattern of findings is suggestive of some central nervous system involvement.

Problems seem to center on her management in classroom and home environments and her learning difficulties, especially as they are related to reading.

Generally, we assume that when a child enters first grade he will have certain "pre-academic" skills, such as paying attention, following simple directions, and sitting still for the periods of time necessary for concentration. Regarding peers, he will have learned to share, to take turns and to "cooperate" in a variety of ways. If certain of these skills have not been mastered, classroom operations will be chaotic; much "deviant" behavior will be demonstrated, and the child will be rejected by peers. While it is tempting to classify these children as emotionally disturbed, what they need most is training in the skills they lack. Such skills are best taught by the teacher — defining, for herself, what is necessary and acceptable behavior and what is deviant behavior and then rewarding appropriate behavior with praise and attention in order to reinforce it, while at the same time ignoring deviant behavior or punishing it where there is no reasonable alternative. Deviant "unacceptable" behavior is often persistent because it is inadvertantly strengthened through the teacher's attention via sympathy or punishment as well as by attention on the part of the peers.

Whenever such deviant behavior develops we are faced with the difficult but possible project of starting at the child's level and reinforcing simple adaptive skills to build an increasingly large adaptive repertoire while at the same time diminishing negative maladaptive behavior. Ultimately the child learns that sufficient attention can be obtained through the practice and performance of adaptive skills and that attention-seeking through deviant behavior is less necessary.

Mrs. Tressel

Would you approve of her being put in a small group such as we now have for special learning problems?

Dr. Ireton

These children tend to be disturbed by large classrooms, not because they have short attention spans but because they are distractible. Although she was perfectly cooperative and paid attention when I tested her, she might not have done this if something had been going on next door. If she functions well in a large regular classroom, fine; if not, a less distracting environment should be arranged.

Mrs. Judy Edmands*

Generally understanding and expression of language appeared to be adequate for her age level. Behavior was characterized by some inattentiveness and distractibility, and she seemed rather tense and uncomfortable.

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*Speech Pathologist, University of Minnesota Hospitals.

Visual-Perceptual Development. There were no obvious perceptual deficits; figure-ground discrimination was excellent for her age level. However, in the other areas of visual-perceptual development she did not perform as well as might be expected considering her general intellectual level. Visual motor coordination form constancy (ability to recognize a circle as a circle no matter what the size, color, etc.) was her poorest area of performance. Ability to judge position in space and spatial relationship was also somewhat below her age level. It was my opinion that these performances could have been affected either by a developmental delay related to central nervous system immaturity or by anxiety.

Reading. No formal rating was done of grade-level reading ability. However, it was obvious that she did not read up to age or grade level.

Visual recognition of alphabet letters (both capital and small) presented no difficulty for her. However, analysis of phonic abilities revealed practically no ability to associate the phonetic sounds with a letter (either vowel or consonant) unless the phonetic sound was the same as the name of the letter.

Impressions and suggestions:

1. There were no obvious perceptual deficits, although development in areas of visual motor coordination form constancy and understanding of directional and spatial relationships seemed not as mature as might be expected.
2. Most obvious deficit in reading skill was lack of phonetic knowledge.
3. Any efforts at remedial reading help should be aimed at (a) a complete analysis of phonetic knowledge and a due and organized attack on that area of reading skill, and (b) a progressive program of activities designed to promote understanding of direction and positions in space and relationships of things in space.

The work should be done on a one-to-one (tutoring) basis if possible.

Dr. Defoe

In summary, this is an eight-year-old girl with a neonatal history of cyanotic spells and minor seizures, subtle neurologic deficits, and an abnormal electroencephalogram suggesting fairly definite (although of minimal intensity) organic brain dysfunction. This may contribute directly to the hyperkinetic behavior and adjustment problems which promoted the referral. However, there is evidence in the family and total environmental history which suggests certain environmental factors as major contributors to her hyperkinesia. It is unlikely the medication she is receiving is contributing significantly to her welfare other than through placebo effect. The recent progress noted in modification of her behavior is more likely attributable to the understanding approach taken within the school and the parental guidance obtained through Lutheran Welfare. It is logical she should be weaned from the drug over the next few months. Efforts in family support and counseling should be continued along with maintenance of a school environment which maximizes feedback for positive and minimizes feedback for negative behavior. Lutheran Welfare is making a significant contribution to the family from the standpoint of support and disciplinary guidance and

Continued

should continue to play the primary role here. All are in agreement that the present approach as outlined by the school is sound.

The parents have expressed enthusiasm for having Dr. Havel function as the professional who should offer total ongoing medical support and guidance. We are pleased to have him here today to contribute and carry away the content of the conference for interpretation to the parents. We will not plan to see the patient at the University Hospital again unless further consultation is deemed advisable by Dr. Havel.

Edward C. Defoe, M.D.
Conference Moderator

Reference

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Trends in Neurological Therapy

November 9-11, 1966

A continuation course in Trends in Neurological Therapy will be presented by the University of Minnesota from November 9 to 11, 1966, at the Nolte Center for Continuing Education. This course is designed to bring the practicing physician up to date on the newer diagnostic and therapeutic measures available for the evaluation of neurologic disorders. Particular attention will be directed towards the management of the patient who has had a stroke or a similar chronic neurologic disorder.

Guest speakers will be *Doctors Simon Horenstein,* Assistant Professor, Division of Neurology, Western Reserve University School of Medicine, Cleveland, Ohio; *M. Wright Van Allen,* Associate Professor, Department of Neurology, State University of Iowa College of Medicine, Iowa City, Iowa; and *Charles Van Buskirk,* Neurologist, York, Pennsylvania.

The course will be presented under the direction of *Doctors A. B. Baker,* Professor and Director, Division of Neurology; and *Robert W. Soll,* Instructor, Division of Neurology. The remainder of the faculty will include members of the faculties of the University of Minnesota Medical School and the Mayo Graduate School of Medicine. Tuition: $75.00. Approved A.A.G.P. hours: 20.

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Coombs Test*

An antibody test used to detect sensitized blood cells in erythroblastosis fetalis and to diagnose other hemolytic syndromes.

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*See page 1571

Medical Seminar

Thrombophlebitis and Embolic Phenomena in Pregnancy

Relationship to the Clotting Mechanism

Presented as a Seminar
Sponsored by
The Faculty of the Mayo Graduate School of Medicine

THROMBOEMBOLIC DISEASE in obstetric patients, with its possible serious consequences for both mother and baby, presents a challenge to the physician.

Ullery[1] has said, "Until recently little could be done for thrombosis except to observe with respect and humility the devastating effects of this disease." However, with the discovery of anticoagulant drugs and the aid of new laboratory methods as well as the advancement in surgical techniques, much progress has been made in the prevention and treatment of thromboembolism.

Virchow,[2] in 1856, pointed out that three things were important for intravascular clotting: (1) stasis of blood flow, (2) injury to the vascular endothelium, and (3) hypercoagulability (increased clotting tendency).

Since obstetric patients meet all these predisposing requirements, it is not surprising that thrombophlebitis is a fairly frequent complication of the pregnant state.

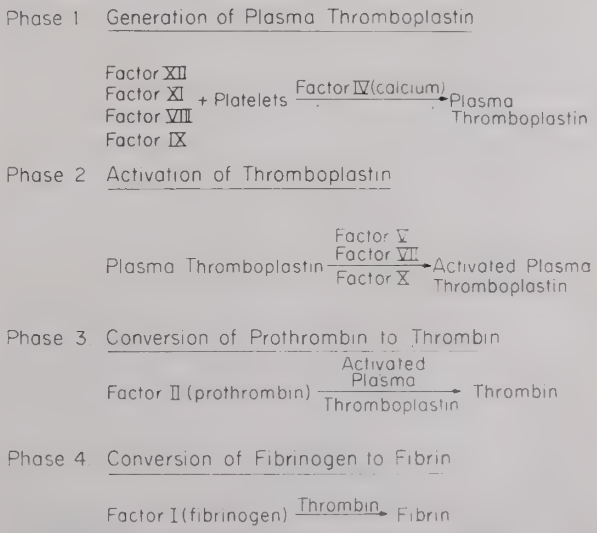
Current Concept of Blood Coagulation[3,4]

In the light of present knowledge, clotting can be considered to occur in four steps: phase 1, generation of thromboplastin; phase 2, activation of thromboplastin; phase 3, conversion of prothrombin to thrombin, and phase 4, conversion of fibrinogen to fibrin. A more detailed consideration of the various coagulation factors is necessary in order to understand the action of the anticoagulant drugs (Figure).

In the first phase, coagulation is initiated in the presence of calcium by the combined action of four prothromboplastic factors (Hageman, PTA, PTC, and AHG) with platelet material (a phospholipid) to form plasma thromboplastin.

In the second phase, the plasma thromboplastin is activated by accelerator factors, V and X. Most investigators consider the stable factor (VII) unnecessary for activation of plasma thromboplastin but necessary for activation of tissue thromboplastin.

Activated thromboplastin as well as calcium is required for the formation of thrombin from prothrombin that occurs in the third phase.


Phase 1 Generation of Plasma Thromboplastin
Factor XII
Factor XI
Factor VIII
Factor IX
+ Platelets
Factor IV (calcium)
Plasma Thromboplastin
Phase 2 Activation of Thromboplastin
Plasma Thromboplastin
Factor V
Factor VII
Factor X
Activated Plasma Thromboplastin
Phase 3 Conversion of Prothrombin to Thrombin
Factor II (prothrombin)
Activated Plasma Thromboplastin
Thrombin
Phase 4 Conversion of Fibrinogen to Fibrin
Factor I (fibrinogen)
Thrombin
Fibrin

Coagulation mechanism. (From Kazmier, F. J., and Spittell, J. A., Jr.: Oral Anticoagulant Drugs. Heart Bull 14:64, 1965, with permission of the publisher, Medical Arts Publishing Foundation.)

Continued

Thrombin, even in trace amounts, finally converts soluble fibrinogen to the insoluble gel fibrin.

It has been said, "When the fact that blood is a suspension of particles in a liquid that contains all the necessary ingredients to change it from a liquid to a solid in a matter of several minutes is considered, one can not be anything but awed at the delicate balance that must exist to maintain its fluidity."[4]

In normal, well individuals there is a perfect balance of the involved factors which encourage or prevent the clotting of blood so that its fluid state is maintained; but in other individuals, because of changes in this mechanism, a hypercoagulable state is reached.[5]

The Relationship of Coagulation Factors and Pregnancy

Clotting Factors

Most investigators agree that certain coagulation factors increase in concentration as pregnancy progresses. Todd and associates[6] found, in 43 coagulation studies on 28 women at various stages of pregnancy, a marked increase in activity in factors VII and X and a moderate increase in concentration of fibrinogen.

Pechet and Alexander[7] reported that factor IX was also increased in pregnancy.

The higher the concentration of factors V, VII, or X, either individually or collectively, the shorter is the prothrombin time.[6] The increases in these clotting factors and the changes in fibrinogen, fibrinolysin, platelets, and phospholipids constitute a truly hypercoagulable state in a pregnant woman and provide an ominous setting for thromboembolism.[7]

It has been stated[8] that all the factors that require vitamin K for their synthesis and are depressed by coumarin compounds — namely, factors II (prothrombin), VII (stable factor), IX (plasma thromboplastin component), and X (Stuart-Prower factor) — are increased during pregnancy.

The clotting defect induced by coumarin and indandione is identical to that seen in vitamin K deficiency.[5] This suggests that oral anticoagulants and vitamin K are competitive. Also, vitamin K is used as an antidote for the oral anticoagulants and restores the prothrombin level to normal in three to six hours.[3]

In pregnancy, factors IX, X, VII, and II are increased.[6-8] These same factors are dependent on vitamin K for synthesis,[5] and these are the factors depressed by coumarin drugs.[5,9]

Quick Test

The one-stage prothrombin test of Quick measures the time required for a fibrin clot to form after the addition of thromboplastic material and calcium ions to oxalated plasma.[3] Normally, formation of the fibrin clot requires 12 to 19 seconds, the time depending on the thromboplastin used. If only calcium ions are added, 90 to 110 seconds are required for the clot to form.

The prothrombin test does not reflect any changes in the clotting activities of the first phase, including factor IX. However, other studies of the clotting factors affected by oral anticoagulants have shown that factor IX closely parallels factor VII. Therefore, because the one-stage prothrombin time accurately demonstrates changes in factor VII, it is believed that the Quick test continues to be a reliable test of anticoagulant effect.[3,4]

Other Predisposing Factors in Pregnancy

In addition to the increased clotting tendency in pregnancy, other circumstances predisposing to thromboembolic disease are those that produce stasis, such as prolonged rest in bed, immobility of the lower extremities, tight abdominal binders, pressure on the popliteal spaces from improperly fitted leg holders or stirrups, obesity, and varicose veins.[5] Other factors are anesthesia, infection, dehydration, nutritional deficiencies, anemia, and hemorrhage.[1,4]

In Ullery's[1] report of 172 cases of thromboembolic disease in the Pennsylvania Hospital, 77% had a hemoglobin value of 9.4 Gm. or less, thus emphasizing the importance of anemia as a predisposing cause. He also found that the hazard of venous thrombosis is increased after abdominal delivery or any difficult operative procedure such as version or midforceps. The incidence of venous thrombosis was also greater for patients who had had general anesthesia. Pulmonary embolism was diagnosed in 17% of the cases. None of the patients treated with anticoagulants died.

Management

It is Ullery's[1] opinion that elevation of the extremity, heat, and elastic bandages may be used in the treatment of postpartum venous thrombosis, but only in conjunction with anticoagulants or surgery.

Spittell[10] has stated the belief that superficial thrombosis may be treated without anticoagulants. However, if the thrombophlebitis becomes more extensive and progresses in spite of conservative treatment, anticoagulant therapy should be employed. For those with marked periphlebitic reactions, he recommends treatment with phenylbutazone.

Anticoagulants

The problem of using anticoagulant therapy in pregnancy is not one of value — since the value has already been proved in the nonpregnant state — but one of safety.[11]

In the early days of investigation into "spoiled sweet clover disease" of cattle, it was found that calves born of cows fed dicoumarin-containing fodder died of hemorrhage a few hours after birth. Thus, in cattle, the calf was more susceptible to dicoumarin poisoning than was the cow, and the hemorrhage-producing principle was capable of passing across the placental barrier.[12]

Wright[12] reported on nine pregnant patients whose venous thrombosis was treated with dicoumarin and in whom there was careful control of the prothrombin concentration at 30 to 40% of normal. A maximum of 18 days of anticoagulant therapy was adequate to relieve all the symptoms. There was only one infant death. In this case, the anticoagulant had been stopped 48 hours before labor began.

Epstein[13] reported three patients whose pregnancies were complicated by antepartum thrombophlebitis and pulmonary embolism and who were treated with coumarin drugs. In all three patients the pregnancies ended with intrauterine fetal death about five weeks after anticoagulant therapy was instituted.

It has been said that with the use of anticoagulants, the maternal mortality rate has been reduced. However, several authors have reported fetal hemorrhage and loss after such treatment.[5,14]

Aaro and associates[15] reported eight patients with antepartum thrombosis who were treated with anticoagulants for periods that varied from six days to 24 weeks. All eight patients were delivered of normal infants at term. The anticoagulant drug was stopped temporarily prior to labor, and vitamin K_1 was given to two patients to reduce further their prothrombin deficiency.

When oral anticoagulants such as the coumarin drugs are used, careful laboratory control is needed to steer the difficult course between ineffective dosage and a generalized hemorrhagic state. For this reason heparin alone is recommended in the antepartum period if one is not sure of the reliability of prothrombin determination or is not skilled in the use of the coumarin drugs.[11]

In the regulation of anticoagulant therapy, Nichol[16] has suggested a formula whereby the optimal therapeutic range of prothrombin deficiency is between 2 to 2½ times the normal prothrombin time in seconds. If the normal prothrombin time is 18 seconds, the optimal range is 27 to 45 seconds.[4]

In the series of Aaro and his associates[15] of 38 postpartum patients with deep venous thrombosis, all of whom were treated with anticoagulants, only one patient had significant postpartum vaginal bleeding. The prothrombin time of this patient was in normal therapeutic range (25% of normal). She was given vitamin K_1 as one of the therapeutic measures in order to help control her bleeding.

Of equal importance as an effective anticoagulant is heparin,[2,4] a mucopolysaccharide. Heparin acts immediately on contact with blood: (1) It forms an antithrombin that neutralizes thrombin and therefore inhibits the conversion of fibrinogen to fibrin; (2) it has an inhibitory action on the earlier stages of clotting; (3) it prevents the

Continued

agglutination of platelets; and (4) it carries a strong, negative electric charge which may be protective against thrombosis. Its anticoagulant effect is based on interference with the function of the coagulation factors rather than a depression of their concentration. Because of its higher molecular weight, heparin probably does not cross the placental barrier. Heparin must be given parenterally and its duration of action is short. At the Mayo Clinic it is given intravenously every four hours and is mainly used in the initiation of anticoagulant therapy or in short-term anticoagulant treatment. Its effect is measured by the whole-blood coagulation time. Protamine sulfate is used as an antidote to bring the coagulation time to normal.

Dextran

Recently, there have been reports of the use of dextran of high molecular weight (75,000) in order to prevent clot formation. Studies at the University of Maryland[17] have shown that dextran is very effective if used in the early stages of the disease but that it is much less satisfactory if the thrombophlebitis has been present for more than 48 hours.

In one report,[17] 39 patients with acute thrombophlebitis were given dextran. Thirty-five had dramatic improvement of symptoms within 24 hours, after which time they could walk without discomfort.

Sawyer and associates[17] suggested that infusion of dextran into the circulation causes physical changes in the blood and vascular system that prevent thrombus propagation and may hasten thrombus resolution. The amounts of dextran used do not result in any bleeding tendencies; so it is not necessary for clotting times to be measured or other laboratory procedures to be made on patients receiving dextran. Only a single administration in 24 hours is required.

Fibrinolytic Agents

The primary function of fibrinolytic agents is to promote the rapid dissolution of an intravascular thrombus.[18] However, the clinical trials of this form of treatment so far have been disappointing. There is also some toxicity shown in the form of mild-to-severe febrile response,[19] along with chills, nausea, vomiting, and hypotension. These fibrinolytic agents have not yet found a place in routine management.[4,19]

Thrombophlebitis

According to Mahorner,[20] venous thrombosis can be classified functionally into three groups: (1) superficial (involving the great and small saphenous veins); (2) deep — this type is potentially lethal — (involving the sural, popliteal and femoral, and ileofemoral veins); and (3) pelvic (in puerperal sepsis).

Superficial Thrombophlebitis

The characteristic appearance[10] is a red, painful, tender, nodular, or linear area. The thrombosed vein can be felt as a raised cord.[4]

In his discussion following the paper by Sawyer and associates,[21] Lilly suggested immediate surgical treatment for this condition. He stated that proximal interruption of the superficial vein should be done as an emergency procedure. This would prevent the development of a propagating thrombus; such a thrombus has occurred in a small percentage of cases.[22] Interruption[21] at the junction between the saphenous and femoral veins can be done under local anesthesia in a few minutes. The patient has a three-hour hospital stay and can return to work the next day.

Sawyer and his associates[21] have noted that patients who have had thrombophlebitis are prone to recurrence and have suggested that a single episode of superficial phlebitis in a leg is a reasonable indication for surgical excision of the involved saphenous veins.

Deep Thrombophlebitis[4,10]

Sural Veins. — Thrombophlebitis that involves the veins of the calf muscles is characterized by pain and tenderness and slight enlargement of the calf. Homan's sign (discomfort on forced dorsiflexion of foot) is positive. From his phlebography investigations, Bauer[23] concluded that 98% of the thrombosis of deep veins begins in the veins of the calf.

Popliteal and Femoral Veins. — Thrombophlebitis of these veins is usually an extension of sural thrombophlebitis, and the findings are similar, along with increased edema and tenderness on palpation of the popliteal space and frequently over the distal portion of Hunter's canal. The leg below the knee is enlarged, and the superficial veins are prominent.

Iliofemoral Veins. — In thrombophlebitis of these veins there is moderately severe pain in the thigh and groin and throughout the entire leg. The superficial veins are distended; the entire leg is enlarged, and the skin may be slightly cyanotic.[4,10,14]

When iliofemoral thrombophlebitis occurs in the postpartum state, this is the familiar "milk leg" or phlegmasia alba dolens.[24] Mahorner[20] stated the belief that when this is diagnosed, prompt operation is indicated, with incision of the femoral vein, removal of the clot, and restoration of the venous flow. Heparin is given intravenously. There is a dramatic relief of symptoms, and good results have been reported. However, McCallister and co-workers[25] evaluated the results of medical therapy in 132 patients with ileofemoral thrombophlebitis who were seen at the Mayo Clinic from 1950 through 1959. This medical treatment consisted of rest in bed, administration of anticoagulants, elevation of leg, warm stupes, and elastic supports. The comparison of the reported results of the treatment with thrombectomy indicates that the incidence of thrombophlebitic sequelae is similar whether patients are treated conservatively or with thrombectomy.

Other surgical procedures used for the purpose of preventing pulmonary emboli are ligation of femoral vein, ligation of the vena cava, and plication of the vena cava.[26,27] However, these are major procedures — often with unfortunate sequelae such as incapacitating venous insufficiency, edema, and leg pains — and they are reserved for instances when more conservative measures have failed.

Pelvic Thrombophlebitis

Collins and associates[28] have reported good results from ligation of the vena cava in women with pelvic venous thrombosis associated with puerperal sepsis.

Pulmonary Embolism

Although part of the treatment for deep venous thrombosis aims at preventing a pulmonary embolus, sometimes the first sign of thrombotic disease is pulmonary embolism.

In 100 autopsies involving dissections of the veins of the pelvis and lower extremities, McLachlin and Patterson[29] observed that, in every case in which a pulmonary embolus was found, a gross thrombus was demonstrated in the veins of the pelvis or lower extremities.

Depending on the size of the embolus, the clinical manifestation of pulmonary embolism may vary from slight pleuritic pain or hemoptysis with restlessness to sudden crushing pain beneath the sternum with dyspnea, cyanosis, and shock.

Wingate[30] wrote that pulmonary embolus is one of the first conditions to be considered in the differential diagnosis on the sudden onset of breathlessness in a pregnant or postpartum patient.

The treatment of pulmonary embolism should include the measures outlined for deep venous thrombosis. Oxygen is indicated for respiratory difficulty and atropine is helpful to relieve the bronchial spasm.[10]

Anticoagulant treatment is started with heparin and should be continued until the prothrombin time is within therapeutic range after therapy with oral anticoagulants has been instituted. Treatment with anticoagulants should be continued for several days after the patient is ambulatory.

Pulmonary embolectomy — the Trendelenburg operation — using the cardiopulmonary bypass is done occasionally.[17] Selection of patients for this operation depends on the accuracy and promptness of diagnosis and the availability of operative facilities and personnel for immediate operation. A ligation of the vena cava is done at the same time in order to prevent further emboli from forming.

Because of the serious consequences of thromboembolic disease, the best treatment of this disease is prophylactic.

Summary

Significant thrombophlebitis occurring

Continued

during and after pregnancy should be treated promptly with local heat, rest in bed, elevation of the extremity, and anticoagulants. Other methods of treatment such as use of dextran, thrombectomy, venous ligation, embolectomy, and fibrinolytic therapy are of limited or questionable value.

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GREEN MEDICINALS*

Herbs for the Heart

Ecclesiasticus said: "The Lord hath created medicines out of the earth and a wise man will not abhor them."

For the heart, the blood, and its circulation herbalism prescribes daisy wine to be prepared as follows:

Daisy Wine

Over four quarts of daisies, picked off the stalks, pour one gallon of boiling water. Let it stand at night, then drain the liquid off and boil it for ten minutes. When it is lukewarm add one yeast cube, dissolved in a little warm water, two lemons and two oranges sliced, a cupful of raisins and three pounds of white sugar. Cover the crock with a cloth and let it stand three weeks to ferment. Skim it, strain and bottle it. In about a month it can be used. — The Gentle Art of Cookery

Other plants beneficial to the circulatory system are acanthus, cucumber, hawthorne, lettuce, nasturtium, olive leaves, and sow thistle.

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*See Minnesota Med 49:1395, 1966.

Drive Safely

Every motorist should remember it is better to be late than to be *the* late. — Springfield Republican

Antibacterial Management of Infection Due to Gram-Negative Bacilli *

Part VI. Some Infections of the Nervous System, Skeletal System, Hematopoietic System, Skin, and Soft Tissues and Comment*

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TUBERCLE BACILLI excluded, the most common bacterial causes of meningitis are meningococci, pneumococci, and type b *Haemophilus influenzae.*[1] Influenzal meningitis is uncommon in persons over 10 and rare in those over 20 years old. Meningitis due to Enterobacteriaceae is common in infants but is uncommon in adults in the absence of penetrating trauma to the central nervous system or underlying diseases such as diabetes and lymphoma. Enterobacteriaceae are responsible in about 75% of cases in neonatal meningitis, and of these *Escherichia coli* is most common. Meningitis from Mimeae organisms is rare. Smears of spinal fluid may indicate a particular regimen, but until cultural reports are available, combined penicillin-G chloramphenicol-sulfonamide therapy has given good coverage. Some workers have used only penicillin and chloramphenicol under such circumstances, and ampicillin alone is currently being investigated in this regard. If *H. influenzae* is causative, chloramphenicol or a combination of streptomycin and a tetracycline is often used, but ampicillin warrants further investigation; the sulfonamides are not commonly used in the definitive treatment of influenzal meningitis today. Management of meningitis due to Enterobacteriaceae depends on the in-vitro susceptibilities; and streptomycin-tetracycline, chloramphenicol, kanamycin, ampicillin, cephalothin, polymyxin B, or colistin may have use. In meningitis from *Pseudomonas,* polymyxin B, or colistin is the drug of choice. In meningitis from Mimeae a tetracycline combined with kanamycin or with polymyxin B, or with colistin is considered.

Cerebritis, brain abscess, and spinal epidural abscess of nontuberculous origin are most often due to staphylococci; however, enterococci and gram-negative bacilli can be causative and, among the latter, *Bacteroides* organisms are not rare. Combined penicillin-G kanamycin-chloramphenicol therapy may be given until microbiologic data are known. Cerebritis may resolve with antibiotic treatment if it is begun early enough. About 10 days are required for encapsulation of a brain abscess and, preferably, surgery is deferred until such is likely. Antibiotic therapy usually is continued for two to three weeks after operation in patients having brain abscess or spinal epidural abscess.

Cavernous sinus thrombosis is rarely due to *H. influenzae* and, in such cases, chloramphenicol has been preferred. Ampicillin warrants investigation.

Although so-called hepatic encephalopathy does not represent an infection of the central nervous system, it is theorized that the condition reflects increased levels of ammonia in the blood since this product of the activity of the intestinal flora on dietary protein may be absorbed systemically from the intestine

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See Part V, Minnesota Med 49:1163, 1966.

**Mayo Clinic and Mayo Foundation: Section of Medicine.

without hepatic detoxification. As aforementioned, neomycin, kanamycin, and paramomycin are the three antibacterial agents most commonly given by the oral route in attempts to decrease the activity of intestinal bacteria in this regard. More recently, alteration of the intestinal flora has been attempted by oral administration of *Lactobacillus* organisms in the form of acidophilus milk. Hypothermia decreases ammonia formation in the intestines of experimental animals and may have potential clinical use in selected cases.

Some Infections of the Skeletal System

Acute Bacterial Arthritis

Acute bacterial arthritis — tuberculosis and specific diseases excluded — is most commonly due to staphylococci, streptococci, and Enterobacteriaceae.[2] Therapy with cephalothin or the conjoint use of a semisynthetic antistaphylococcal penicillin and colistin provide initial coverage. When microbiologic data are known, therapy is modified accordingly. *H. influenzae* may be causative in children, and among the regimens which may have use are streptomycin-tetracycline, chloramphenicol, ampicillin, or cephalothin. If, within 72 hours, the infection has not responded dramatically, surgery is probably required.

Chronic Bacterial Arthritis

In chronic bacterial arthritis, antibacterial therapy is usually ineffective unless bony fragments and fibrous tissue can be removed. When further operation is inappropriate, instillation of proteolytic enzymes may help remove detritus and cleanse the region to allow less hindered action of antibiotics given locally and systemically. Good results are also described with use of local antibiotics in a detergent solution; the penetrating action of the detergent may enable the antibiotics to reach bacteria buried in pus and necrotic tissue. The solution containing the antibiotics and the detergent is irrigated intermittently either by syringe or by an electrically driven suction pump. Hyperbaric oxygenation may have application in the management of certain chronic skeletal infections. Regional perfusion via arterial and venous catheters of such agents as neomycin and colistin is being investigated.

In brucellar osteomyelitis, synovitis, and bursitis, streptomycin-tetracycline is effective when combined with aggressive surgical treatment.[3] In brucellar spondylitis, the antibiotic regimen without surgical intervention may suffice. Acute hematogenous osteomyelitis due to type b *H. influenzae* has been described. Use of ampicillin should be considered.[4]

Intervertebral Disk Infection

Infection of an intervertebral disk after urologic instrumentation appears to result from septic emboli lodging in the spinal column via the vertebral venous plexus. Staphylococci, Enterobacteriaceae, or *Pseudomonas* organisms are commonly responsible. In some patients, abdominal pain may overshadow the distress in the back. Pain may precede roentgenographic evidence of spinal disease by several days or more. A semisynthetic penicillin such as nafcillin plus colistin gives initial coverage if such appears desirable.

Some Infections Associated With Hematopoietic Diseases

Leukemia, lymphoma, multiple myeloma, aplastic anemia, and agranulocytosis predispose to bacteremia due to gram-negative bacilli.[5] In acute leukemia, chronic myelogenous leukemia, aplastic anemia, and agranulocytosis, deficiency of effective neutrophils may be responsible. In chronic lymphatic leukemia, lymphoma, and multiple myeloma, there may be lack of efficient gamma-globulin. In some cases iatrogenic factors such as therapy with adrenocorticosteroids, radiomimetic drugs, and irradiation may be causative. A possible additional factor in some leukemic patients, especially those having chronic lymphatic leukemia, may involve impaired phagocytosis of the leukocytes; however, the impaired phagocytosis may represent a serum (? globulin) defect. Regimens such as nafcillin-streptomycin-tetracycline or penicillin-G kanamycin-chloramphenicol give initial coverage. However, if response is incomplete after 12 hours or so, polymyxin B or colistin is often substituted for streptomycin and kanamycin because of the propensity for pseudomonal bacteremia to develop. Also, since polymicrobic bacteremia is not rare among these patients, penicillin-G or an allied drug is often given initially.

As aforementioned, patients having certain underlying conditions such as sickle-cell disease, Hodgkin's disease, and liver disease may thereby be predisposed to infection from *Salmonella* organisms.

Hypogammaglobulinemia

Hypogammaglobulinemia, unassociated with such diseases as lymphoma, leukemia, and myeloma, may be characterized by increased susceptibility to infection. Among these infections, those of the respiratory tract are often caused by various cocci, but *H. influenzae* has also been implicated, especially in patients having an acquired form of the defect. In the latter patients, administration of gamma-globulin and perhaps conjoint use of a tetracycline or ampicillin may be helpful.

Contaminated Transfusions

Transfusion of contaminated blood is fatal to more than 50% of recipients, and the mechanism of death usually is profound, persistent shock. Contamination of banked blood most commonly is due to endotoxin-producing gram-negative bacilli which grow well at refrigerator temperatures. A centrifuged sample of the blood when smeared and gram-stained will reveal the organisms. Vasopressors and tetracycline-streptomycin or chloramphenicol-kanamycin is given immediately. Renal shutdown is common.

Splenectomy

Because splenectomy has been performed in the management of certain hematopoietic diseases such as thrombocytopenic purpura and congenital hemolytic anemia, the question has arisen whether the patient is thereby predisposed to infection. Studies in this regard were initiated because it was feared that infections, especially those involving the bloodstream, might prove overwhelming in the absence of the clearing function of the spleen. It appears to be the current consensus that the underlying disease for which splenectomy had been performed, rather than the absence of the spleen, is more likely responsible for any increased incidence of infection. In those conditions for which splenectomy may be performed and which do not intrinsically enhance the likelihood of infection, the incidence and extent of future infections may not differ significantly from normal.

Some Infections of the Skin and Soft Tissues

Synergistic bacterial gangrene may be caused by a microaerophilic streptococcus plus either *Staphylococcus aureus* or gram-negative bacillus. Some workers believe that *Streptococcus pyogenes* alone is capable of causing a gangrenous reaction and that the additional organisms which may be cultured represent contaminants.[6] Regimens such as nafcillin-tetracycline or penicillin-G chloramphenicol give coverage until microbiologic data are known.

Peripheral Gangrene

Multiple peripheral gangrene,[7] wherein rapid necrosis of acral parts (most commonly digits) occurs, can be of varied causes. Vascular diseases, hematologic abnormalities, ergotism, cold injury, and numerous other causes may be responsible, but one should also consider overwhelming infection. Diphtheria, as well as meningococcal, pneumococcal, rickettsial, and tuberculous infections have been causative, but endocarditis due to gram-negative bacilli, cholera, and shigellosis must be considered.

Cellulitis

Cellulitis most commonly is streptococcal or staphylococcal in origin but on rare occasions is caused by other organisms including type b *H. influenzae*.[8] Influenzal cellulitis is more likely to occur in children, usually involves the face, and may leave a characteristic bluish-purple discoloration. Bacteremia is

Continued

usually present, and often nose and throat cultures are also positive for *H. influenzae*. Combined streptomycin-tetracycline therapy or use of chloramphenicol or ampicillin is considered.

Tularemia

Cutaneous tularemia reflects contact with the carcasses of wild animals, particularly rabbits, or with a biting arthropod, usually a tick or fly, and the appearance of a skin ulcer within 48 to 72 hours. Tender regional lymph nodes and fever are characteristic. Conjunctival or nasopharyngeal involvement, pneumonia, and bacteremia may occur. Classically, streptomycin is recommended, but one of the tetracyclines is often used in ambulatory patients. When at least 10 days of therapy is given, relapse is rare. A persistent or recurrent bubo may require surgical drainage.

Rat-Bite Fever

Rat-bite fever is of two pathogenic types: that caused by *Streptobacillus moniliformis* and that also known as sodoku which is caused by various spirilla, including *S. minus*. In the United States, the streptobacillary type is more common. The disease may occur after the bite of an infected animal such as a rat, mouse, cat, dog, or weasel. In addition to the local lesion, the two pathogenic types usually share the common manifestations of chills, rash, and intermittent fever. Streptobacillary infection also occurs via the gastrointestinal tract, and is known as Haverhill fever, as when contaminated milk is ingested. Streptobacillary infection may be complicated by endocarditis, arthritis, pulmonary infection, and abscess formation. Complications, including endocarditis, are rare in the spirillary form. In both streptobacillary and spirillary infection, penicillin is preferred, but streptomycin, a tetracycline, or erythromycin may also be effective.

Superficial Ulcers

Superficial ulcers such as those of the lower extremities are of multiple origin — for example, from trauma, varicose veins, and ischemia. Numerous organisms, such as *Staphylococcus* and *Pseudomonas*, may take up residence and it is often difficult to assay their clinical significance. Antibacterial therapy varies with the individual case and the microbiologic findings. Some authorities advise against local antibacterial therapy since it may incite an allergic reaction, thereby aggravating the lesion. Systemic antibacterial therapy in selected patients may help control spreading or ascending infection and contribute to the salvage of a limb or permit amputation at a lower level. Bacteremia is an occasional complication.

Wound Infection

Postoperative wound infections are usually due to *S. aureus*, but Enterobacteriaceae and *Pseudomonas* organisms sometimes require use of pertinent drugs when they appear to represent significant invasion. The more toxic agents like streptomycin, kanamycin, and chloramphenicol are avoided if possible. One is also reluctant to employ a tetracycline because of the conjoint or potential presence of staphylococci. Cephalothin and colistin are often considered if microbiologic data indicate their applicability.

Burn Infections

In victims of severe burns, in addition to debridement and various isolation procedures, numerous regimens have been proposed to lessen the likelihood of infection. Weekly use of a vaccine of heat-killed phenol-preserved *Pseudomonas* plus daily use of hyperimmune plasma from previously vaccinated persons constitute such a regimen. Immersion in silicone fluid and use of silicone-soaked dressings is another. Treatment with dressings kept wet with a 0.5% solution of silver nitrate and changed once or twice daily, combined with intermittent baths in Locke's solution, has its advocates.[9] Exposure, occlusive dressings, and topical application of various antibacterial agents, including sulfonamides, are among the therapeutic techniques advised by other workers. Surface cooling, instituted as soon as possible after the burn and continued for at least 30 minutes, may decrease local reaction to the injury. Systemic antibacterial therapy appears best limited to the first few days and is to be given thereafter only when there are proper clinical and microbiologic indications. It may be that bacteremia due to *Pseudomonas* organisms, staphylococci and so forth, occurs because antibiotic-induced floral changes encourage the invasion of these resistant organisms when unnecessarily prolonged systemic antibacterial therapy is given. Local and systemic use of gentamicin is being investigated against *Pseudomonas* infection.

Comment

In the preceding two decades, advances have been made in the treatment of infections due to gram-negative bacilli, and consequently there is available a more satisfying approach to the individual problem at hand.

In the management of infections due to gram-negative bacilli, in addition to microbiologic considerations, the individual situation may influence selection of the drug to be used; vomiting may disallow use of usual therapy if that therapy ordinarily is given orally. Previous untoward reactions or current intolerance of an agent may disqualify it for use.

Combinations of antibacterial agents should be reserved for situations demanding coverage while microbiologic data are awaited, for polymicrobic infections, and for instances of infections in which there are indications that an enhanced effect is possible. The use of multiple agents in the definitive management of infections due to gram-negative bacilli not only is unnecessary in many cases, but may increase bacterial resistance more than if patients were treated with a single drug. Indiscriminate use of multiple agents may increase bacterial resistance, since such resistance appears to be a direct function of the total amount of a given antibacterial drug used in a given community.

Before antibacterial drugs can become effective, surgical procedures such as drainage of an abscess are occasionally necessary. Adequate surgical attacks in such cases may bring about cure of an infection, but more often eradication of pathogens requires conjoint antibacterical therapy.

Impaired renal function makes mandatory the careful use of certain drugs that are either nephrotoxic or potentially toxic to other organ systems. When resistant organisms are encountered, the intrinsic severity of the infection is the key for deciding whether the risk associated with the use of more toxic antibacterial agents is justified. If renal function is less than normal, the doses of such drugs should be correspondingly reduced.

It should be constantly recalled that antibacterial agents are a mixed blessing because, in addition to resulting in untoward reactions, they may cause emergence of resistant organisms, their use may result in a diagnostic loss if they are employed before diagnosis is established, and they are expensive.

Adequate management of infection due to gram-negative bacilli requires close cooperation between the clinician and the microbiologist. Careful clinical and microbiologic analysis of the individual infection and the use of discrimination in attempts at therapy are mandatory; there is little place for diagnostic or therapeutic dogma in the management of serious infections due to gram-negative bacilli. It may be necessary at any stage in the management of gram-negative bacillary infections to re-evaluate, re-examine, and alter the regimen.

Not all infections due to gram-negative bacilli can be eradicated any more than can all disease in any sphere of medical endeavor. Failure in the management of a given patient should prompt consideration of the nature of a possible underlying lesion, since certain diseases like leukemia, multiple myeloma, and metastatic malignancy, which are likely to be complicated by infection due to gram-negative bacilli, may make recovery impossible. The prognosis may also be influenced by the duration of infection before institution of appropriate management, and the occurrence of complications such as endotoxin shock and superinfection. In regard to superinfection, periodic microbiologic study of the sputum and stools during ther-

Continued

apy may reveal floral changes in time to avert clinical manifestations of superinfection.

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Medical Men and Music*

"I could not stamp out the intense love of music which at my birth was implanted in me. I whistled as a child early, and at all times. My earliest impressions were of the notes I produced; they came as freely as they came from the bobolink who, dancing on the dry mullein stalk, warbles forth his rich notes in our spring days."**

Thus did the eminent clinician, Henry Ingersoll Bowditch (1808-1892), reminisce on his boyhood. Though he never learned to play an instrument, having once tried the bassoon and failed to elicit more than a few whoops thereon, appreciation of music was his lifelong joy and inspiration.

Among earlier medical men who loved music was physician Felix Platter (1536-1614) of Basel, who collected instruments and performed proficiently on several of them, among which was the lute, wherewith he serenaded his sweetheart.

Seventeenth century medical men noted for their love of music included Hermann Boerhaave (1668-1738) of Leyden and John Arbuthnot (1667-1735), Alexander Pope's medical advisor, who composed sacred anthems, one of them the still extant "As Pants the Heart." Of Boerhaave one of his biographers says:

"When business was over, he took the exercise of riding or walking, and when weary, revived himself with music, his most delightful entertainment, being not only a good performer on several instruments, particularly the lute, which he accompanied also with his voice, but a good theorist likewise in the science, having read the ancient and best authors on the subject, as appears by the lectures he gave on sound and hearing."**

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*See Minnesota Med 49:1363, 1966.

**Music and Medicine, Edited by D. Schullian and M. Schoen, Henry Schuman, Inc., New York.

In order to form an immaculate member of a flock of sheep one must, above all, be a sheep. — Albert Einstein

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References: (1) Based on 23 clinical papers, 1512 cases. Bibliography on request. (2) Bush, I. M., Orkin, L. A., and Winter, J. W., in Sylvester, J. C.: Antimicrobial Agents and Chemotherapy—1964, Ann Arbor, American Society for Microbiology, 1965, p. 722.

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Grand Rounds

*Intestinal Amebiasis**

WILLIAM TORP, M.D.
Medical Resident

OF THE SEVERAL species of amebae which inhabit the G.I. tract of man, only one, Endamoeba histolytica, is pathogenic. In spite of this the diagnosis may be quite difficult to establish, and the investigator may find this ameba to be extremely elusive.

Amebiasis, intestinal and extra-intestinal, has virtually a world-wide distribution but is most prevalent in subtropical and tropical environs, especially in areas where the populace lives under primitive conditions.

Incidence

Incidence of the disease in the United States has been the subject of some discussion (Table 1). McGoth, in 1960, published results of a study done at the Mayo Clinic in which he arrived at an average figure of 2.1 percent over a 20-year period, with annual incidence varying from 1.1 to 3.8 percent.[2] This was based on findings of stool examinations in patients with gastrointestinal symptoms, approximately 3 percent of the Mayo Clinic patient load from 1937 to 1957. Sepulveda from the University of

TABLE I
Incidence of Intestinal Amebiasis in the United States

1913	Giffin — Mayo Clinic	1,700 patients	4.6%
1916	Sanford — Tulane	5,000 patients	10.7%
1923	Boech and Stiler Federal and State Hospitals	8,000 patients	4.1%
1926	Craig — United States		10.0%
1938	Kessel and Sinitsin Los Angeles	2,016 patients	3.3%
1951	Craig and Faust		8.1%
1952-53	Mayo Clinic	1,773 patients	1.3%
1937-57	McGoth — Mayo Clinic		2.1%

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*Presented as a Medical Grand Rounds at Hennepin County General Hospital, June 7, 1966.

Continued

Mexico states that 15 to 30 percent of the adult population in Mexico has intestinal amebiasis.[3] Many of these people are asymptomatic. Faust, in a study done in Columbia, reports an incidence of 33.5 percent positive stool specimens in 651 low-income city dwellers over a five-month period. None of these had a frank case of amebic dysentery.[4] In contrast to this he found the incidence of positive stool specimens to be 6.4 percent among 93 patients in a private clinic. Elsden-Dew reported an incidence of approximately 26 percent in a study from Durban, South Africa.[5] Armas-Cruz reports an incidence of almost 40 percent based on a two-year study of 3,500 clinic patients in Chile.[6]

It is apparent from these figures that the incidence of amebiasis in the United States is probably much lower than the stated 10 percent and that the incidence in endemic areas is quite high.

The Organism

While man has been troubled with dysentery for centuries it has been only in the past 90 years that E. histolytica has been identified as one of the causes. In 1870 amebae were found in the stool of cholera patients, but no etiological relationship was established.[4] A few years later Losch, in Russia, found amebae containing red blood cells in the stool of a patient with "relapsing dysentery". He then produced dysentery in dogs by giving dysenteric stool by mouth and rectum. He also observed the organism in autopsy specimens but did not make the observation that these amebae, which he called "Amoeba coli", were the causative agents of the disease. At the turn of the century Endamoeba histolytica and Endamoeba coli were differentiated, and in 1913 Walker and Sellards, working in the Philippine Islands, showed that E. histolytica would produce dysentery in some volunteer patients while E. coli would not.[7]

In 1919, Dobell described and illustrated five species of ameba found in man,[7] only one of which, Endamoeba histolytica, is pathogenic. Some of the characteristics of these organisms are shown in Table 2. If the trophozoite forms are preserved well enough to be active, the diagnosis can be made on this basis. However, identification of cysts is usually easier.

The life cycle of E. histolytica is interesting and should be understood. Man, several species of monkeys, dogs and rats may serve as natural reservoirs for this organism, and the kitten, guinea pig, hamster and rabbit are all good laboratory hosts.[1,5]

Mode of Infection

In order to become infected one must ingest the cystic form which, with proper environmental conditions, can be very hardy. The cyst passes to the proximal portion of the small bowel where the cyst wall is discarded and the metacyst emerges. A short time later the cytoplasm divides and each of the nuclei forms very small metacystic trophozoites. These reach the cecum and may invade the mucosal layer causing tissue infection. They continue to multiply by binary fission. The trophozoites may continue moving through the large bowel, and as the stool becomes dehydrated the organism eliminates all undigested inclusion bodies and takes on a round form, the precystic stage. It then forms a thin covering around itself and becomes a cyst. The single nucleus that is present divides until there are four nuclei, and the cyst is then said to be mature. This maturity may take place in the rectum or after the stool has been passed. It is interesting to note that trophozoites in diarrhea stools do not encyst.

The trophozoites usually invade the intestinal mucosa between rugae, in the lumen of a vertical gland or between glands. They then migrate toward the muscularis mucosae, at the same time establishing a pyramidal-shaped colony. The opening on the surface is usually quite small and discrete and may be hemorrhagic or have a large amount of exudate. They are easily visible to the naked eye. Cross section of the ulcer shows much more activity than appears evident from the surface.

Bacterial Flora

There seem to be other factors necessary for infection in addition to ingestion of material containing amebic cysts. It is apparently important to have certain bacterial flora present. Raffensperger relates an experiment done by Westphal in 1937 in which he swallowed washed cysts of E. histolytica. He showed cysts and trophozoites in his stool in two days but did not develop any symptoms until after he ingested 50 cc. of ameba-free stool suspension from a patient with amebic dysentery.[7] Phillips and his associates go so far as to say that more widespread use of broad-spectrum antibiotics may be partially responsible for some decline in incidence of the symptomatic disease.[9] In a study of stool specimens from 1773 hospital patients and staff, they demonstrated E. histolytica in 23. Of these 23 persons, 22 had no previous exposure to broad-spectrum antibiotics. This was compared to 100 with negative stools, 12 of whom had previous broad-spectrum antibiotics.

TABLE 2

Ameba Found in Human G.I. Tract

Name	Stages	Trophozoite	Cyst
E. histolytica	5 (Trophozoite, pre-cystic, cystic, meta cystic, meta cystic trophozoite)	Large race 18-30 micra Small race 9-15 micra May contain bacteria, leukocytes or RBC. Rapid protruding and retracting of pseudopodia.	11-18 micra 6-11 micra 1-4 nuclei depending on maturity
Endamoeba coli	3 (Trophozoite, pre-cystic, cystic)	20-30 micra Pseudopodia small, blunt and not as prominent as E. histolytica. Slow movement, may contain bacteria but usually no RBC.	12-35 micra 1-32 nuclei
Endolimax nana	3 (Trophozoite, pre-cystic, cystic)	6-15 micra	7-8 micra oval shape 1-4 nuclei
Iodamoeba butschlii	2 (Trophozoite and cystic)	10-15 micra	Single nucleus irregular shape
Dientamoeba fragilis	1 (Trophozoite only)	8-9 micra Active	

Continued

Dietary Influence

Elsden-Dew in his study of amebiasis in South Africa found that among the Indians and Europeans the disease was asymptomatic or mild, while in the African it was acute and fulminant.[5] He feels that this may be due to dietary differences in that the Africans he studied had diets with much maize and little milk. He also refers to a study done on two communities in Tennessee, both of which used large amounts of corn in the diet, but one of which had milk and vegetable supplements. The latter group had a much lower incidence of acute amebiasis than the other group. Elsden-Dew feels that the areas of the world with high incidence of amebiasis are also areas in which corn is a major part of the diet.

Trauma to Intestines

It has also been shown that traumatizing the bowel may make a laboratory animal more susceptible to infection. Faust makes the point that travelers may make themselves more amebiasis-prone by eating new types of fruits or condiments or by taking abnormal amounts of alcoholic beverages, causing irritative trauma to the bowel.[1]

Infested Food

The disease is spread directly by several vehicles. Prior to the Chicago epidemic in 1933, water was not considered a source of contamination and most attention was focused on infected food handlers.[10] This epidemic resulted in at least 52 deaths and complete revision of the plumbing in the hotel which was the source of infection.

Other modes of transmission include vegetables fertilized with human excreta, flies, cockroaches, fomites and clothing.

Diagnosis

Diagnosis can be extremely difficult. Not only can the organisms be very difficult to isolate and identify, but the clinical picture of the disease may be extremely variable.

Armas-Cruz reports that less than 10 percent of the patients in his study with positive stool specimens for E. histolytica showed clinical signs of the disease.[6] Faust did not have a frank case of dysentery in a group of over 200 with positive stools.[4] Many of the cases in Table 1 were picked up on routine studies of stool specimens in asymptomatic persons.

Most of the published series referred to in this paper had very rigid criteria for diagnosis. All emphasized the need for expert staff in interpreting findings in stool specimens, biopsy material, rectal smears, etc.

For diagnosis Juniper[11] required active colonic ulceration with acute symptoms which responded to anti-amebic therapy and typical trophozoites on a permanent stain prep. Fifty-two of his patients had diarrhea with eight to 20 stools per day; 33 had gross, bloody stools, and 22 had stools with blood-streaked mucous. The three patients without diarrhea had several formed stools per day. Many had other gastrointestinal symptoms which included mild nausea and vomiting, abdominal cramps, and weight loss averaging 20 pounds.

Proctoscopy and Biopsy

Proctoscopic examination was done on 46 patients, 40 of whom showed scattered ulcerations in otherwise normal appearing mucosa. Rectal biopsy was done on 22 of the 46 proctoscopic examinations; on 18 of these trophozoites were demonstrated.

In an earlier report on use of rectal biopsies, Juniper cited 14 cases, all of which were positive.[12] He emphasizes the necessity for care in handling and fixing the specimen. It is extremely important to study the exudate overlying the ulcer, as this is where trophozoites are most commonly found. The patient should not have an enema before the proctoscopy and the biopsy, as the exudate will be washed out. Serial sections were done on the biopsy material in spite of the fact that all but one of the patients had trophozoites on a single slide. Half of the patients showed trophozoites in all 15 of the serial sections of the biopsy.

The recommended method of obtaining exudate from a rectal ulcer is to scrape the surface or to use suction and a small pipette.

Ellenberg published a report on sigmoidoscopic findings in 176 symptomatic and asymptomatic cases and found typical lesions in 125 of the 176 patients.[13]

Stool Examination

In examining stool specimens care must be taken to get a proper sample. If stool is formed one will find cysts only; if the stool is dysenteric E. histolytica will be in the trophozoite stage. Faust states that unformed stool must be examined within one hour and preferably within thirty minutes so that trophozoites will still be mobile. Formed stools on the other hand may be held for 24 hours at 70 degrees F. or for seven to 10 days in refrigerator without affecting the characteristics of the cyst. Faust states that the yield of a positive result on a single specimen is not more than 20 to 27 percent; but using a concentrating technique with zinc sulfate can double this yield. Because trophozoites and cysts are not excreted in a uniform manner, Faust recommended examination of three to four stool specimens which are passed every second or third day for better and more reliable results.

Saline purge may be helpful if the lesions are primarily in the cecum, as the trophozoite may disintegrate rather than encyst during passage through the large bowel.

Laboratory Procedures

Culture methods are available, but the technique is apparently quite difficult even in expert hands. Juniper was unable to culture the organism in any of a series of 27 documented cases of amebic colitis.[11]

Complement fixation titers are also available but the method is apparently still somewhat experimental.

Barium enema may be helpful. Juniper had positive results in eight of 28 patients (ulceration, ameboma, conical spasticity of the colon).

Non-specific findings that may be helpful include mild fever, mild elevation of the white count, mild anemia. There may be a slight increase in eosinophils.

Treatment

The methods of treatment of intestinal amebiasis are many and varied and depend on whether a patient is an asymptomatic carrier or is having an acute episode.

Continued

There are three categories of drugs used in treatment: (1) tissue amebicides, (2) those amebicides which act mainly in the gut, and (3) broad-spectrum antibiotics. Common tissue amebicides are emetine and chloroquine, while diiodo-hydroxyquinoline (diodoquine) and the arsenical derivatives (e.g., carbarsone) act mainly in the gut. Wilmot presents a very concise view of these agents in Current Therapy.[14] Emetine has some definite drawbacks in that it is toxic to myocardium and other muscle; but it is none the less used by many investigators.

Tissue Amebicides

Wilmot suggests using one of the amebicides which acts in the gut for treatment of an asymptomatic patient. He makes the point that most cases of amebiasis will have parasites in the tissue as well as in the gut and therefore must be treated with that in mind. For amebic dysentery he recommends either a regimen in which tetracycline, diodoquine and chloroquine are given simultaneously; otherwise, emetine, tetracycline and diodoquine are used. Juniper suggests a similar program but feels antibiotics are not routinely indicated.[11] In his study of 55 patients in which 54 were treated, there were six deaths, with the rest responding to therapy.

Elsden-Dew, in Africa, uses emetine during the hospital stay, and the patient is discharged on carbarsone.

Amebicides Acting in the Gut

Most[15] recommends use of an amebicide that acts in the gut for the asymptomatic carrier and mild case. He feels diodoquine is best and gives a 75 percent cure. Carbarsone may be used if necessary. For the acute case he gives emetine and tetracycline followed by diodoquine and then by chloroquine to remove any ameba in the liver not eliminated by emetine.

Antibiotics

There has been some discussion as to whether antibiotics (namely tetracycline) have a place in this therapy.[11] Juniper feels that they should be reserved for control of symptoms in children when they are unable to take the oral arsenicals. Most also reserves antibiotics for the more severe cases, while Wilmot uses them more liberally.

The feeling has been that tetracycline, probably the most commonly used antibiotic, acts on the intestinal flora only; but McHardy and Frye in 1954 did some in-vitro studies which showed that fumagillin, carbomycin and tetracycline had some direct action on the ameba.[16] Fumagillin acts directly on the organism and has no antibacterial effect. McHardy showed excellent results with fumagillin in a study of 175 patients.[17] The drug is not widely used today; this may be partially due to its side effects of gastrointestinal symptoms and skin eruptions.

Complications

Complications of the disease include extra-intestinal infection, bleeding, perforation and stenosis.

Kean analyzed 149 of the 240 fatal cases of amebiasis from the Armed Forces Institute of Pathology.[18] It is interesting to note that a correct clinical diagnosis was made in only one third of the cases prior to death, and of those with liver abscesses only half were recognized. The causes of death are summarized in Table 3.

Most common extra-intestinal sites of infection are (in descending order) the liver (acute amebic hepatitis and abscess), the lungs and pleura, the intracranial areas, and the skin, although these are extremely rare.

Summary

In summary, we have a disease which is caused by a protozoan, the identification of which is often difficult. The severity of the disease may vary from that of an asymptomatic carrier to that of acute, fulminating, possibly fatal proportions. It may be successfully treated with a combination of amebicidal drugs, one of which acts in the gut and the other in the tissues. Tetracycline may be used against ameba in the gut. Extra-intestinal infections may occur and require more rigid therapy than that outlined above. This disease continues to be a major public health problem in undeveloped areas of the world as well as in any area where proper sewage disposal is not carried out.

Case Report

The patient, a 22-year-old negro female, stated that she was feeling well until approximately one year prior to admission when she developed diarrhea during an illness which she called "flu". She was having up to ten stools a day which she described as watery and varying in quantity. The stool pattern persisted through her time of admission. Four months after her onset of diarrhea the patient noted bloody stools which varied in color from light red at onset to dark red at time of admission. During this time she has had a 32-pound weight loss and intermittent episodes of nausea and vomiting.

She has been living in Minneapolis but has visited Chicago and Denver. She is not aware of any exposure to infectious disease. She admits to smoking one package of cigarettes and drinking one bottle of beer each day. Her eating habits have been irregular.

Physical examination showed a thin, negro female. Proctoscopic examination revealed grossly normal mucosa with the exception of many small, punctate craters,

TABLE 3*
Cause of Death in 148 Cases of Amebiasis

Intestinal	
Perforation	45
Dysentery	21
Hemorrhage	5
Abscess	2
Obstruction	1
Surgery	6
	80 (54%)
Liver Abscess	
Without rupture	19
Rupture into abdomen	12
Lung involvement	17
Pericarditis	2
Subdiaphragmatic abscess	2
Surgical drainage	4
	56 (38%)
Miscellaneous	
Brain abscess	6
Emetine myocarditis	2
Other	2
	10 (7%)
Not Stated	2 (1%)

*From Kean et al.

Continued

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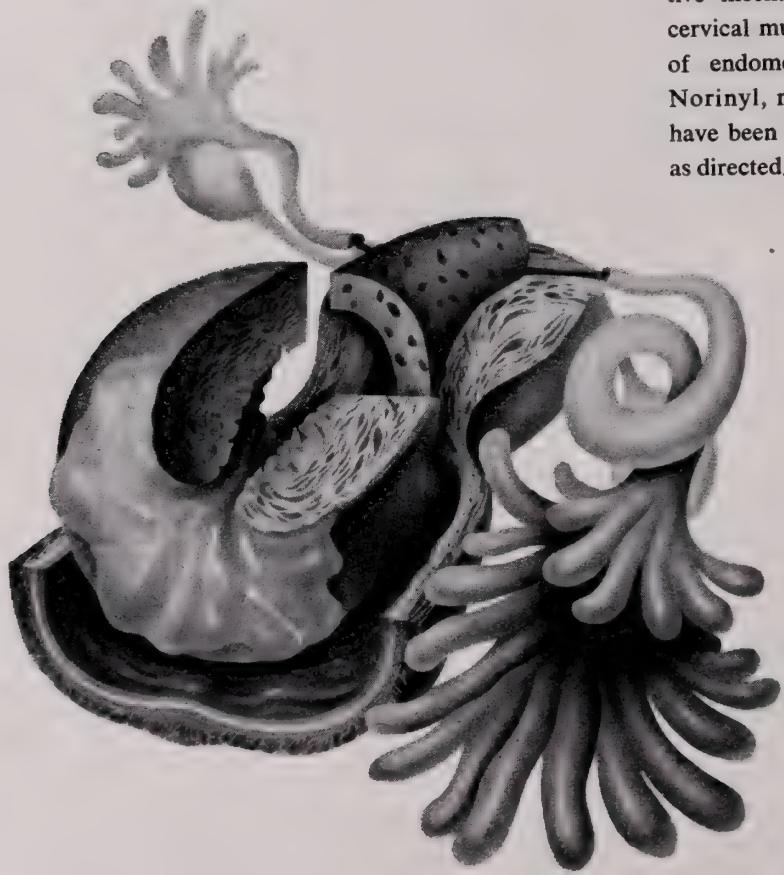

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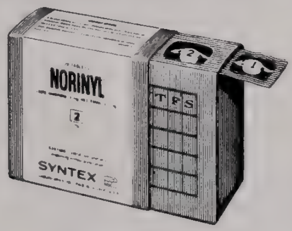

Contraindications: Thrombophlebitis or pulmonary embolism (current or past). Existing evidence does not support a causal relationship between use of Norinyl and development of thromboembolism. While a study which was conducted does not resolve definitively the possible etiologic relationship between progestational agents and intravascular clotting, it tends to confirm the findings of the Ad Hoc Advisory Committee appointed by the Food and Drug Administration to review this possibility. Cardiac, renal or hepatic dysfunction. Carcinoma of the breast or genital tract. Patients with a history of psychic depression should be carefully studied and the drug discontinued if depression recurs to marked degree. Patients with a history of cerebral vascular accident.

Warning: Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Precautions: By May 1963, experience with norethindrone 2 mg.—mestranol 0.1 mg. had extended over 24 months. Through miscalculation, omission or error in taking the recommended dosage of Norinyl, pregnancy may result. If regular menses fail to appear and treatment schedule has not been adhered to, or if patient misses two menstrual periods, possibility of pregnancy should be resolved before resuming Norinyl. If pregnancy is established, Norinyl should be discontinued during period of gestation since virilization of the female fetus has been reported with oral use of progestational agents or estrogen. When lactation is desired, withhold Norinyl until nursing needs are established. Existing uterine fibroids may increase in size. In metabolic or endocrine disorders, careful clinical preevaluation is indicated. A few patients without evidence of hyperthyroidism had elevated serum protein-bound iodine levels, which in the light of present knowledge, does not necessarily imply hyperthyroidism. Protein-bound iodine increased following estrogen administration. Bromsulphalein retention has occurred in up to 25% of patients without evidence of hepatic dysfunction. Studies from 24-hour urine collections have shown an increase in aldosterone and 17-ketosteroids and decrease in 17-hydroxycorticoid levels. Thus, Norinyl should be discontinued prior to and during thyroid, liver or adrenal function tests. Because progestational agents may cause fluid retention, conditions such as epilepsy, migraine and asthma require careful observation. Thus far no deleterious effect on pituitary, ovarian or adrenal function has been noted; however, long-range possible effect on these and other organs must await more prolonged observation. Norinyl should be used with caution in patients with bone, renal or any disease involving calcium or phosphorus metabolism.

Side Effects: Intermenstrual bleeding; amenorrhea; symptoms resembling early pregnancy, such as nausea, breast engorgement or enlargement, chloasma and minor degree of fluid retention (if these should occur and patient has not strictly adhered to medication plan, she should be tested for pregnancy); weight gain; subjective complaints such as headache, dizziness, nervousness, irritability; in a few patients libido was increased. In a total of 3,090 patients, 2.2% discontinued medication because of nausea.

NOTE: See sections on contraindications and precautions for possible side effects on other organ systems.

Dosage and Administration: One Norinyl tablet orally for 20 days, commencing on day 5 through and including day 24 of the menstrual cycle. (Day 1 is the first day of menstrual bleeding.)

Availability: Dispensers of 20 and 60 tablets; bottles of 100.

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Laboratory findings: hemoglobin 11.5, wbc. 8,800, 41 neutrophils, 50 lymphocytes, and 9 eosinophils. MCV. 90. MCHC. 29. Total eosinophils 609/mm^3. E.S.R. 19. Barium enema negative. Stool for ova and parasites negative on five examinations including one zinc flotation method. Rectal biopsy read as "nonspecific colitis". Exudate from a rectal ulcer bed revealed E. histolytica.

Hospital course: The patient was started on a course of tetracycline, 250 mg., q6h, for a two-week period. Approximately three weeks after discharge she had a negative proctoscopic examination and was having a single bowel movement per day.

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3. Frye, W. W.: Current Gastroenterology, New York, Paul B. Halber, Inc., p. 559, 1962.

Oliver Wendell Holmes on Elbow Grease

You are now fresh from the lecture-room and the laboratory. You can pass an examination in anatomy, physiology, chemistry, materia medica, which the men in large practice all around you would find a more potent sudorific than any in the Pharmacopoeia. These masters of the art of healing were once as ready with their answers as you are now, but they have got rid of a great deal of the less immediately practical part of their acquisitions, and you must undergo the same depleting process. Hard work will train it off, as sharp exercise trains off the fat of a prize-fighter.

Medical Men on Postage Stamps*

Andreas Vesalius (1514-1564), Dutch physician who modernized anatomy by his 'odious' dissection of human bodies and so revolutionized the practice of surgery, was honored for his achievements by the issuance of a commemorative Belgian postage stamp in 1964.

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*See Minnesota Med 49:1360, 1966.

A nation that cannot trust its intellectuals cannot trust itself. —

A. Whitney Griswold, late president of Yale University

Book Reviews

That is a good book which is opened with expectation and closed with profit. —
Alcott

HERITABLE DISORDERS OF CONNECTIVE TISSUE — Book Review, McKusick, Victor A., Third Edition, C. V. Mosby Company, St. Louis (1966).

This is an exceptional book which is worthy of study by any practitioner of medicine, be he a generalist or specialist, a researcher or clinician. The author attempts and succeeds in correlating widely scattered clinical observations on the inherited disorders of connective tissue, i.e., the Marfan syndrome, osteogenesis imperfecta, alkaptonuria, pseudoxanthoma elasticum, the mucopolysaccharides — and other rarer syndromes. The multitude of observations from all areas of clinical medicine and research, as well as genetics and pathology, make the book of widespread interest for all practitioners of medicine. In particular, specialists in internal medicine, pediatrics and general practice will find the book to be valuable. The correlation of the complications and variations in these diseases and the many excellent photographs and illustrative case histories make reading or scanning this book a pleasure.

Those readers who read the first two chapters on the clinical behavior of hereditary syndromes and the biology of the normal connective tissue as well as the detailed discussions of the diseases will become convinced of Dr. McKusick's conviction "that clinical investigation of pathological states is as legitimate a method as any other for studying biology". Hopefully, they will be encouraged to make further observations and ultimately, contributions to the literature on these or other diseases.

The final virtue of this excellent book is the comprehensive bibliography which accompanies each of the diseases discussed. These bibliographies make it possible for anyone interested in further study to have easy access to the important literature on each of these diseases.

Warren J. Warwick, M.D.
Minneapolis, Minnesota

TWINS: TWICE THE TROUBLE, TWICE THE FUN — Betsy Holland Gehman, J. B. Lippincott Co., Philadelphia and New York, 1965, 223 pages.

This field manual for mothers of twins cascades from the pen of Betsy Gehman — a former woman's magazine editor. She wrote it, she says, because there were few books to consult when she struggled with the problems of her own twins. Out of her experiences Mrs. Gehman welds a personal and practical guidebook for distraught or curious mothers. She devotes about one third of the space to the medical aspects of twins. The high-spirited, spockian narrative rests on well ordered facts sifted from experts. Statistical probabilities, physiology of fraternal and identical twins, techniques of breast feeding, articles in medical periodicals — all come under maternal scrutiny. Physicians who treat or advise mothers of twins will enjoy the book.

Carl O. Rice, M.D.
Minneapolis, Minnesota

FERMENT IN MEDICINE: A STUDY OF THE ESSENCE OF MEDICAL PRACTICE AND ITS NEW DILEMMAS — Richard M. MaGraw, W. B. Saunders Co., Philadelphia and London, 1965. 273 pages, $8.50.

Richard MaGraw, a psychiatrist and internist, who heads the Comprehensive Care Clinic at the University of Minnesota, generates both heat and light in this blunt dissection of modern medicine. MaGraw sallies forth with a series of vignettes on such sensitive issues as financial third parties, fragmented care by specialists, doctor-administrator conflicts, the town-gown muddle, the dimming of professional prestige, the impact of automation, and the encroachment of government.

The picture that MaGraw paints is not flattering. Medicine emerges as a ponderous, shambling creature who has had blinders on in the past and is nearsighted for the future. Through all discussions runs the recurrent theme that times have changed and that doctors will have to resolve their grief complex about loss of status if they are to effectively contribute to society and medicine.

The ideas for this book were born and nurtured during 15 years of giving seminars for medical students. At times, MaGraw's academic idealism outruns his tact. Many practitioners will find the book's professorial flavor distasteful and unrealistic. Those active in medical politics will probably be offended. But most doctors, I believe, will admire MaGraw for his courage in speaking his mind. He is a provocative critic whose facts are well ordered and well documented. The book ends with a frankly emotional appeal for a new set of attitudes by the next leaders of medicine.

Richard L. Reece, M.D.
Minneapolis, Minnesota

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Contraindications: Contraindicated in individuals who have shown hypersensitivity to any of its components. Not recommended for prophylaxis or in the management of infectious processes which may require more than 10 days of continuous therapy. If clinical judgement dictates therapy for longer periods, serial monitoring of liver function is recommended. Not recommended for subjects who have shown abnormal liver function tests, or hepatotoxic reactions to triacetyloleandomycin.

Precautions and Adverse Reactions: Triacetyloleandomycin, administered to adults in daily oral doses of 1.0 gm. for 10 or more days, may produce hepatic dysfunction and jaundice. Adults requiring 3 gm. of Signemycin initially should have liver function followed carefully and the dosage should be reduced as promptly as possible to the usual recommended range of 1.0 to 2.0 gm. per day. Present clinical experience indicates that the observed changes in liver function are reversible after discontinuation of the drug. Use with caution in lower than usual doses in cases with renal impairment to avoid accumulation of tetracycline and possible liver toxicity. If therapy is prolonged under such circumstances, tetracycline serum levels may be advisable. In long term therapy or with intensive treatment or in known or suspected renal dysfunction, periodic laboratory evaluation of the hematopoietic, renal and hepatic systems should be done. Formation of an apparently harmless calcium complex with tetracycline in any bone forming tissue may occur. Use of tetracycline during tooth development (3rd trimester of pregnancy, infancy and early childhood) may cause discoloration of the teeth. Reversible increased intracranial pressure due to an unknown mechanism has been observed occasionally in infants receiving tetracycline. Glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis and definite allergic reactions occur rarely. Severe anaphylactoid reactions have been reported as due to triacetyloleandomycin. Photosensitivity and photoallergic reactions (due to the tetracycline) occur rarely. Medication should be discontinued when evidence of significant adverse side effects or reaction is present. Patients should be carefully observed for evidence of overgrowth of nonsusceptible organisms including fungi, which occurs occasionally, and which indicates this drug should be discontinued and appropriate therapy instituted. Steps should be taken to avoid masking syphilis when treating gonorrhea.

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Abstracts, Briefs and Commentaries

FEEDING METHODS

The relation between the feeding method used during infancy and later personality structure has been debated by generations of physicians. Although breast feeding is believed to have psychological advantages over bottle or cup feeding, it is difficult to find evidence to support this view.

Four groups of 20 babies were studied by Drs. Davis and Ruiz. One group was fed by bottle, one by breast, one by cup, and one by mixed methods. Twelve to 18 years later, the subjects (now adolescents) were evaluated on a questionnaire which included requests for information about physical health, height, weight, scholastic achievement, and presence of certain "oral" habits such as eating, drinking, talking, chewing, and smoking. The questionnaire also included three items involving "dependency" strivings, viz., need to be around people, inability to control temper, and submissiveness. Finally, each of the subjects completed a Minnesota Multiphasic Personality Inventory (MMPI).

Extensive analysis of the data obtained did not reveal significant differences among the four groups with respect to physical characteristics, personality type, or academic achievement. No difference with respect to orality or dependency was found between subjects who had sucked as infants and subjects who had been fed by methods that did not allow them to suck. The only significant finding on the MMPI was that cup-fed girls were better adjusted than breast-fed girls; however, this finding must be cross-validated before any inferences can be made. In sum, this investigation provided no evidence that method of feeding during infancy is related to subsequent physical or psychological health.

James Janecek, M.D.*
St. Paul, Minnesota

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*Director of In-Patient Psychiatric Services, St. Paul Ramsey Hospital, Assistant Professor, Department of Psychiatry, University of Minnesota.

Davis, R. E., and Ruiz, R. A.: Infant Feeding Method and Adolescent Personality. Amer J Psychiat 122:673, 1965.

CHRONIC ALCOHOLISM

This article adds another woe to the growing list of potential problems for the heavy drinker. Heretofore, most physicians thought only of the liver as a target area for alcohol.

Continued

Recently heart disease and hypoglycemia were recognized, and now an acute muscular syndrome joins the ranks. The syndrome is made up of muscle aches, cramps, and weakness with variable constellations of laboratory findings—myoglobin and related proteins in the urine; increased serum creatine phosphokinase activity; poor lactic acid response to ischemic exercise; and variable muscle phosphanylase activity. The authors made their observations on 21 patients within 48 hours after acute intoxication. They speculate on the pathogenesis, but conclude their paper by saying that the only established facts are that the syndrome is brought on by heavy drink and is reversed when drinking stops.

Richard Reece, M.D.
Minneapolis, Minnesota

Perkoff, G. T., Hardy, P. and Velez-Garcia, E.: Reversible Acute Muscular Syndrome in Chronic Alcoholism. New Engl J Med 274:1277, 1966.

SPHINCTEROTOMY

A circular band of muscle fibers extending for more than five millimeters longitudinally along the common duct, at the level of the outer fenestra where the duct enters the duodenal wall, is the most important element of the sphincter of Oddi. Sphincterotomy is required occasionally in acute cholecystitis or in patients who have been known to have gallstones for many years, and also when a patient has a post-cholecystectomy syndrome characterized by recurring attacks of pain. The third class of patients includes those who have attacks of recurring pancreatitis associated with biliary tract disease.

The technique of sphincterotomy is described, and it is pointed out that a ureteral catheter is passed preferably through the cystic duct and through the ampulla. A mosquito forceps is then placed through the opening of the sphincter alongside the catheter and the crushed tissue under the mosquito forceps is excised, removing a triangular wedge which includes the choledochal sphincter. On occasions the pancreatic duct can be visualized entering from the left and posteriorly.

Partington obtained good results in approximately 70 percent, fair in 20 percent, and poor results in the remainder. He pointed out that drainage of the common duct is not necessary if the duct has not been opened and if the common duct has been catheterized through the cystic duct.

Carl O. Rice, M.D.
Minneapolis, Minnesota

Partington, P. F., M.D.: Sphincterotomy for Stenosis of Spincter of Oddi. Surg Gynec Obstet 123:2, 282, 1966.

ENDOMETRIAL CANCER

The 610 patients reported were treated for 27 different modalities of cancer. Five hundred seven patients were followed five years or more, with a crude survival rate of 54%. Two hundred twelve patients were treated with preliminary radium followed by hysterectomy, with a five-year survival of 68%; 152 were treated with primary hysterectomy, with a five-year survival rate of 65%. This treatment has been used with increasing frequency in the past decade. The prognosis depends on whether the cancer is confined to the uterus or has gone beyond it. During the 40 years covered by the study, the incidence of cases with disease limited to the uterus has increased from 40% to 70%. The mean age of the patients was 52 years for stage 0 (limited to endometrium) and 59 years for stage 4 (cases with carcinomatosis). The incidence of vaginal metastases had no relation to the use of radium; it was highest in patients with advanced disease. A second malignancy developed in 14 cases.

Courtesy of References and Reviews
Journal of the American Medical Association

Javert, C., and Renning, E.: Cancer 16:1057, 1963.

INFERIOR VENA CAVA

This report shatters the long held belief that inferior vena cava ligation stops pulmonary emboli arising in the legs. In a two and a half year period the authors were confronted with nine patients with recurrent emboli after vena cava ligation. All were documented clinically, and two were confirmed at autopsy. All had typical signs and symptoms of pulmonary embolism; seven had elevated lactic dehydrogenase levels; and all had some form of x-ray confirmation. The group of nine patients represented a recurrence rate of 20 per cent — far above the rate quoted in the literature. Large collateral veins were demonstrated by venography in six patients. These veins were probably the pathway for the recurrent emboli.

Richard Reece, M.D.
Minneapolis, Minnesota

Gurewich, V., Thomas, D. P., and Rabinor, K. R.: Pulmonary Embolism after Ligation of the Inferior Vena Cava. New Engl J Med 274:1350, 1966.

RHINOPHYMA

The terminology, history, pathology, etiology, and treatment of rhinophyma are discussed. Rhinophyma is rare in women. Of 57 patients with rhinophyma 14 were operated on, 2 under local anesthesia and 12 under general anesthesia. Since 2 of the patients were brothers, attention was attracted to the hereditary aspect. Family histories of the other patients, however, were completely negative for rhinophyma. The authors used the simple shaving technique and think that this procedure is safe if care is taken not to expose the underlying cartilages. Subsequent retraction of scar tissue was no problem and if the deformity is not overcorrected during the surgical procedure, the formation of scar tissue will not adversely influence the final result. It is important to bevel the incision around the rhinophyma to avoid a step effect. With this technique, healing occurred smoothly and the transition between the re-epithelialized area and the normal nasal skin became almost undetectable. The entire epithelialization process took about 2 or 3 weeks, at which time the shaved area was covered with a smooth and delicate epithelium. Tissue culture studies of rhinophymatous tissue showed a marked reduction in the onset and speed of growth as compared with normal skin of the same patients. While acne rosacea, seborrhea, and adenoid cystic epithelioma may cause humps and enlargement of the nose, they are considered to be separate and distinct disease processes and are not actual precursors of true rhinophyma.

Courtesy of References and Reviews
Journal of the American Medical Association

Matton, G., Pickrell, K., Huger, W., and Pound, E.: Plast Reconstr Surg 30:403, 1962.

GASTRIC POLYPS

Gastric polyps, either solitary or multiple, have been studied in 14 cases. Three of these were benign, 2 denoted some cellular atypia, 6 revealed carcinoma "in situ," and 3 were invading carcinomas. All but one of the transformed polyps were over 1.5 cm. in diameter. The association with other primary carcinoma was encountered in two patients, and one patient had the association of benign polyposis with pernicious anemia. If only the glandular polyps are included in the material one gains the impression that gastric polyps are of important interest as a precancerous lesion and should be dealt with as such.

Courtesy of References and Reviews
Journal of the American Medical Association

D'Amours, C., and Bonenfant, J.: Canad Med Ass J 89:23 July 6 1963.

NEWER TREATMENTS OF STROKE

Cerebral infarction due to occlusive vascular disease is being studied enthusiastically with the idea of providing benefit to patients who in the past were considered to be beyond effective medical help.

Anticoagulants, fibrinolytic agents and surgical excision of occlusive lesions in the extra-cranial arteries are the most commonly used procedures in this new approach to the problem of stroke.

Among 73 patients, most of whom were in the sixth decade, there was an operative mortality of 8%, and there was an incidence of complication of 19%. The complications included local hemorrhage, local infection, transient hypoglossal nerve palsy, permanent Horner's syndrome, and postoperative hypotension.

In the mortality figures, it was considered that technical errors, which can now be avoided, were a major factor. For the postoperative thrombosis or embolization that occurred after the operation, it was considered that if cerebral protection can be provided during the clamping of the artery, better results are predictable.

It was suggested that embolization can be minimized by the use of a distal occluding clamp prior to mobilization of the carotid vessel. It was also suggested that the venous oxygen saturation demonstrating the adequacy of cerebral circulation should be practiced meticulously in order to minimize if not completely banish the need for a shunt procedure, which in itself increases the danger of postoperative thrombosis. The use of oxygen-rich gas mixtures, hypercarbia, and system hypertension to 180 mm. of mercury is urged.

Carl O. Rice, M.D.
Minneapolis, Minnesota

Hass, Wm. K., Clauss, Roy H., Goldberg, Arthur F., Johnson, Allan J., Imparato, Anthony M., and Ransohoff, Joseph: The Special Problems Associated with Surgical and Thrombolytic Treatment of Stroke. Arch Surg 92:27, 1966.

Pediatrics

I am an optimist in my philosophy of life. I became a pediatrician because pediatrics is full of interesting and important problems. It has the added advantage of bringing you in contact with youth and its stimulation. Furthermore, children are our future. I have never regretted the step. The more I have studied the child the more I have admired nature for accomplishing this miracle of creation. — Bela Schick

Special Article

Noninvasive Neurological Changes in Systemic Malignancy*

ETER JAMES DYCK, M.D.**
ochester, Minnesota

THIS IS A review of some of the neurological syndromes found to be associated with cancer but in which there is no actual invasion or compression by the tumor of the central nervous system, of peripheral nerves, or of muscle. These neurologic syndromes have only recently been recognized by neurologists, and much of the material in this review comes from a recent monograph edited by Lord Brain and Norris.[1]

Various neurological syndromes have been known to occur in association with malignant lesions; for example, in his textbook, Oppenheim[2] mentioned carcinomatous cachexia as a cause of neuritis. Others have reported cases in which there was both a neurological condition and cancer. In 1929 Casper[3] described a patient who had subacute cerebellar degeneration with carcinoma, and Parker and Kernohan[4] described a similar case in 1933. In 1948 Denny-Brown[5] stated that the coincidence of development of bronchogenic carcinoma in two similar cases of a sensory neuropathy and muscle degeneration "was more than a chance association." According to Lennox and Prichard[6] these cases had been initially reported to the Royal Society of Medicine by Kendall and, subsequently, also by Denny-Brown. Along with a third case, they were also included in Wyburn-Mason's[7] paper in 1948.

Since these early reports, British investigators have reported cases of carcinoma associated with such neurological syndromes as peripheral neuritis, a myasthenia gravis-like illness, and subacute cerebellar degeneration. Lennox and Prichard[6] reviewed the records of 299 consecutive patients with bronchogenic carcinoma at the Hammersmith Hospital and found five who had, in addition, a peripheral neuritis. This incidence, 1.7%, was considerably higher than

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*Read at the meeting of the Minnesota Society of Neurological Sciences, Minneapolis, November 5, 1965.

**Mayo Clinic and Mayo Foundation: Section of Neurology.

Continued

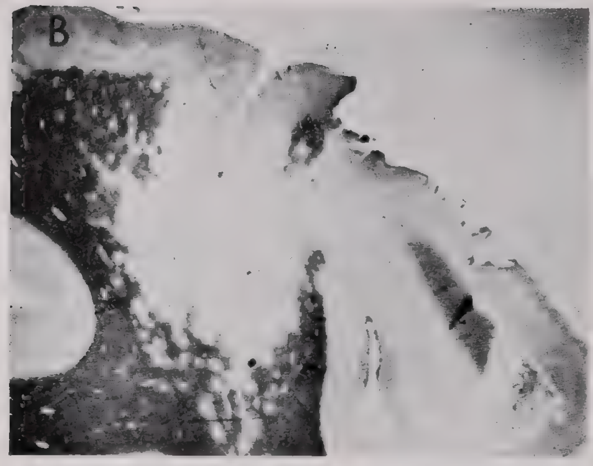

Fig. 1 — Low-power photomicrograph showing multiple foci of loss of myelin; a more destructive lesion, producing cavitation of tissue, is seen within the tangentially-cut gyrus on the extreme right. (Loyez myelin stain.) (From Richardson, E. P.: Progressive Multifocal Leukoencephalopathy. In Brain, Lord, and Norris, F. H., Jr.: The Remote Effects of Cancer on the Nervous System. New York, Grune & Stratton, Inc., 1965, p. 8. By permission of the publisher, Grune & Stratton, Inc.)

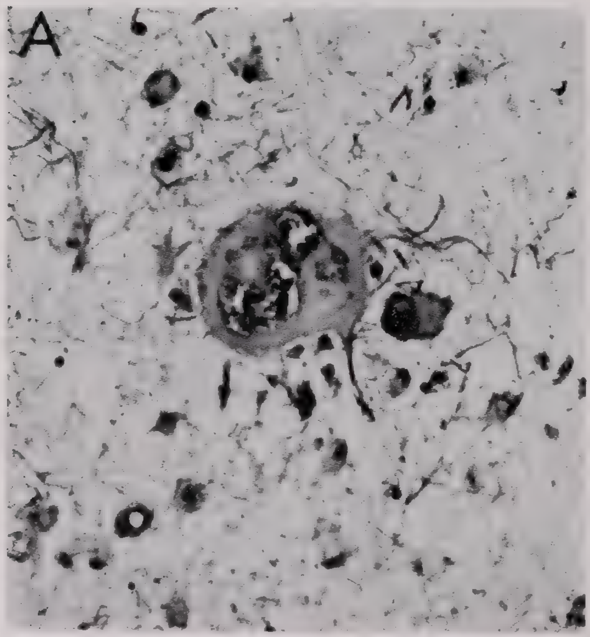

Fig. 2 — Multinucleated giant astrocyte of multifocal leukoencephalopathy. Note typical astrocytic processes and glial fibrils, which identify the cell. (Holzer stain; x135.) (From Richardson, E. P.: Progressive Multifocal Leukoencephalopathy. In Brain, Lord, and Norris, F. H., Jr.: The Remote Effects of Cancer on the Nervous System. New York, Grune & Stratton, Inc., 1965, p. 9. By permission of the publisher, Grune & Stratton, Inc.)

the incidence of neuritis in the general admissions to the hospital. These authors recognized that their argument for an association between these two conditions rested on a statistical basis. In 1956 Lambert and coworkers[8] described a group of patients who had an unusual and distinctive defect of neuromuscular transmission different from myasthenia gravis, and most of whom also had small-cell bronchogenic carcinoma. In 1958 Aström and co-workers[9] described progressive multifocal leukoencephalopathy.*

The interest in the association between certain neurological syndromes and various carcinomas lies not only in the proper identification of these disorders but, more important, in the information it may give regarding the relationship between the carcinoma and the neurological syndrome. The strongest case for a significant relationship can be made when the neurological syndrome itself is distinctive and is always associated in time with one kind of malignancy. Unfortunately, none of the neurological syndromes associated with carcinoma fulfill these criteria completely. The three that seem to come closest are the sensory neuropathy of carcinoma, the myasthenic syndrome of Lambert, Eaton, and Rooke,[8] and the progressive multifocal leukoencephalopathy of Aström, Mancall, and Richardson.[9] It should be pointed out that two of these neurological syndromes cannot be identified with certainty clinically but depend on electrophysiological tests in the case of the myasthenic syndrome and on pathological examination of the brain in the case of the progressive multifocal leukoencephalopathy.

The case for a significant association between other neurological syndromes and cancer seems to be less substantial. The syndromes are in themselves not as distinctive, being seen most frequently associated with diseases other than malignancy. The malignancies with which they are associated are of many types, and there is no correlation between severity of the neurological syndrome and the severity and extent of the malignancy. In these cases the argument for a significant relationship rests mainly on the higher frequency of association between neurological syndrome and malignancy.

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*See Test Your Word Score Page 1573.

Progressive Multifocal Leukoencephalopathy

This condition is discussed first because the criteria, proposed earlier, for establishing an association between malignancy and a neurological syndrome are reasonably well satisfied here, and there is a possible explanation for the mechanism of production of the neurological syndrome.

Neuropathological Findings

The diagnosis of this condition is based on neuropathological findings, as shown in Figure 1. Note the demyelinated white and adjacent gray matter of this coronal section of the cerebral hemisphere, with adjacent smaller areas which are also demyelinated. Occasionally, similar changes have been noted in the spinal cord. Richardson[10] thought that the appearance of the lesion and the clinically progressive course suggest that these smaller lesions enlarge and coalesce. The myelin breakdown is sudanophilic with preservation of the axis cylinders. Striking features are the gigantic astrocytes and the unequivocal multipolar mitotic figures (Figure 2).

Clinical Features

This distinctive neuropathological picture occurs in association with lymphomas in more than one half of all cases (Table). In the remainder of the cases it occurs in association with chronic disease. Furthermore, it appears to be a disease of late adult life. The clinical features are not distinctive except for the rapidly progressive course, of three to six months. Hemiparesis progressing to quadriparesis, visual field defects or blindness, aphasia, ataxia, dementia, confusional state, and, finally, coma are said to be typical manifestations. Certainly, when such a neurological picture is noted in association with lymphoma, the correct diagnosis should be strongly suspected.

Richardson[10] postulated that the most likely explanation of this neurological syndrome is a virus infection. (There is a higher

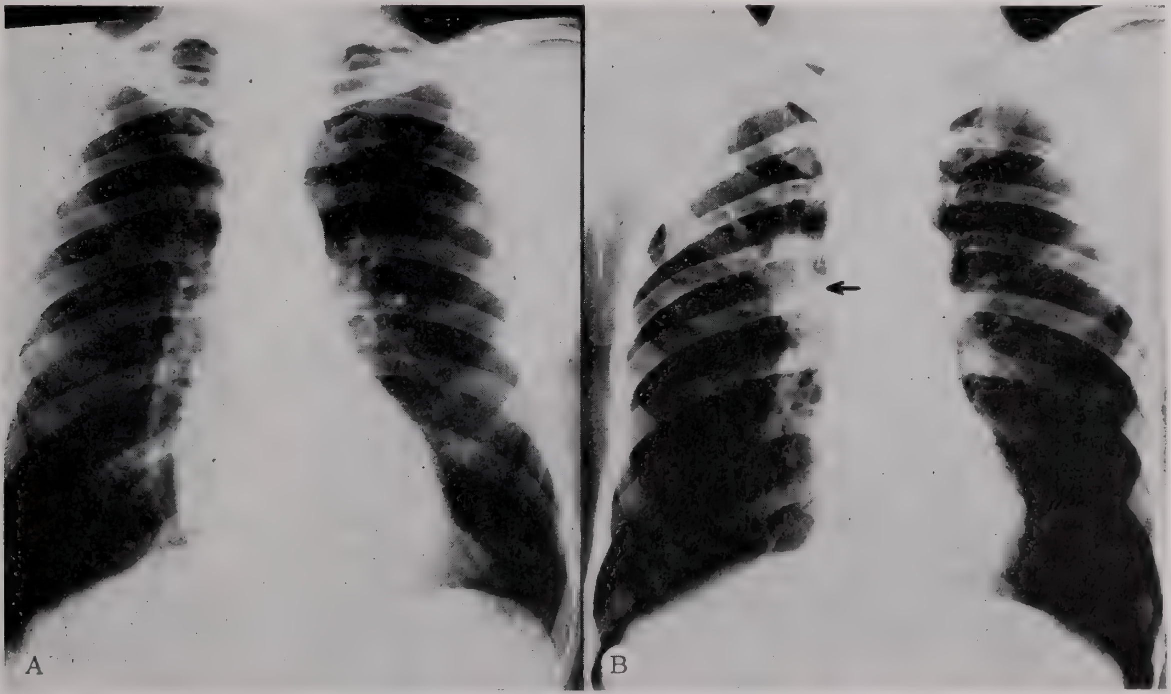

Fig. 3 — *(a)* Normal thoracic roentgenogram 22 months after the onset of the neuropathy. *(b)* Mass in the right hilum apparent 3½ years after the onset of symptoms. (From Dyck, P. J., Bailey, A. A., and Olszewski, Jerzy: Carcinomatous Neuromyopathy: A Case of Sensory Neuropathy and Myopathy with Onset Three and One-half Years Before Clinical Recognition of the Bronchogenic Carcinoma. Canad Med Ass J 79:914, 1958. By permission of the publisher, Canadian Medical Association Journal.)

Continued

incidence of herpes zoster infection [also viral] associated with lymphomas.) ZuRhein and Chou[11] recently reported having seen virus-like particles in oligodendroglial cells from small demyelinated regions in a case considered to be progressive multifocal leukoencephalopathy. The presence of these virus particles in demyelinated regions of the brain in this condition raises the possibility that this demyelinating disorder may be caused by a viral infection. If a virus can be grown from brains in cases of progressive multifocal leukoencephalopathy and if the virus can be transmitted with the production of similar lesions, the viral etiology will be established. However, it is possible that such a virus might not grow except in brain tissue which, biochemically or otherwise, has been altered by the presence of chronic disease such as lymphoma. A baffling point about these cases is the fact that, contrary to what one expects in a viral encephalitis, there is no pleocytosis reflected in the spinal fluid and the time course is different.

Myasthenic Syndrome and Lung Cancer

Lambert and co-workers[8] have defined this syndrome. Of 30 patients who fulfilled the electrophysiological criteria, 22 had, then or subsequently, intrathoracic tumors. Seventeen of 19 bronchogenic carcinomas were of the small cell type — the criteria of a unique syndrome invariably associated with a specific malignancy being almost fulfilled. Furthermore, improvement of the neurological state in association with apparent successful treatment of the bronchogenic tumor has been noted in some of the cases.

Diseases Associated with Progressive Multifocal Leukoencephalopathy*

Disease	Number of Cases	
Lymphoproliferative diseases:		
Chronic lymphocytic leukemia	9	
Hodgkin's disease	7	
Lymphosarcoma	4	
Plasmocytoma (multiple myeloma)	1	
Subtotal		21
Myeloproliferative diseases:		
Chronic myelocytic leukemia	3	
Acute myelocytic leukemia	1	
Polycythemia vera	3	
Subtotal		7
Neoneoplastic reticuloendotheliosis:		
Sarcoidosis	5†	
Tuberculosis	3†	
Primary hypersplenism	1	
Whipple's disease	1	
Subtotal		10
Miscellaneous:		
Carcinomatosis	3	
Pulmonary anthracosilicosis	1	
Senility	1	
Senility; coronary heart disease; splenomegaly of uncertain cause	1	
Hepatosplenomegaly, with liver and adrenal necrosis of uncertain cause	1	
Subtotal		7
Total		45

*From Richardson, E. P.: Progressive Multifocal Leukoencephalopathy. In Brain, Lord, and Norris, F. H., Jr.: The Remote Effects of Cancer on the Nervous System, New York, Grune & Stratton, Inc., 1965, p. 13. (By permission of the publisher, Grune & Stratton, Inc.)

†One patient had both sarcoidosis and pulmonary tuberculosis.

Clinical Features

The clinical features in themselves have not been distinctive enough to permit a firm diagnosis in most cases. The syndrome occurs mainly in men more than 40 years of age; weakness and fatigability are the most common initial symptoms. In contrast to myasthenia gravis, the bulbar muscles are less affected than are proximal limb muscles, and thus diplopia, weakness of facial muscles, and chewing weakness are less dominant symptoms in the myasthenic syndrome. Dryness of the mouth was a presenting symptom in one half of the patients. Peripheral paresthesia and loss of potentia were also found in approximately one half of the patients.

Electrophysiological Tests

On clinical testing of muscle strength it was possible to detect, in some of these patients, the unusually slow buildup of the muscle contraction, developing during one to several seconds. Tendon reflexes tended to be absent or diminished, especially in the lower extremities. Two salient features of the distinctive electrophysiological tests are:

1. The amplitude of the action potential from muscle and the amplitude of the muscle twitch from a single supramaximal stimulus of the appropriate nerve are unusually small, although the voluntary contraction of the muscle is almost normal in strength.
2. At slow rates of repetitive stimulation (three per second) a decrease, from an already low amplitude, in the action potential occurs. However, at rapid rates (at 50 per second) marked facilitation occurs. This facilitation explains the fact that voluntary strength is normal or almost so, but the twitch response from a single electrical stimulus is very low.

Lambert and co-workers[8] thought that this syndrome is best explained by a defect at the neuromuscular junction and, furthermore, that it is distinct from myasthenia gravis both by clinical and by electromyographic features. They found that quanidine hydrochloride has been more effective than anticholinesterases in the management of these cases.

Carcinomatous Sensory Neuropathy

Approximately 10 cases of sensory neuropathy with degeneration of dorsal root ganglion cells have now been described. Dr. William Karnes,[12] a neurologist at the Mayo Clinic, has recently reviewed these and has found a new case. He has not found any reports of this syndrome associated with any condition except bronchogenic carcinoma. From the clinical point of view, these cases have been distinctive enough so that, in some of them, the finding of a bronchogenic carcinoma was anticipated on the basis of the neurological state. It should be pointed out that other varieties of sensory neuropathy, such as familial, diabetic, amyloid, arsenic, and unexplained neuropathies, can simulate this neuropathy; but in these cases the family history, the evident diabetes, the increased excretion of arsenic, or the presence of deposits of amyloid in the dorsal ganglia permits differentiation. In addition, the course of these other sensory neuropathies tends to be much more prolonged.

History and Pathological Findings

The history and pathological alterations of this condition are illustrated by a case (Case 1) reported in 1958 in collaboration with Bailey and Olszewski.[13]

A 49-year-old farmer had progressive, prickling, numbness of his feet and hands for three and one-half years before the first evidence of bronchogenic carcinoma was recognized roentgenographically. Thoracic roentgenograms taken 22 months after the onset of symptoms of the sensory neuropathy did not show the carcinoma (Figure 3*a*), although its presence was anticipated on the basis of the neurological syndrome. Three and one-half years after the onset of the sensory neuropathy, the patient was in a cachectic state and had lost 30 pounds; the thoracic roentgenogram now showed the hilar tumor (Figure 3*b*). He had severe distal numbness and shooting pains in all extremities and, on examination, generalized muscle weakness and wasting, areflexia, and severe distal sensory loss. Death occurred almost four years after the onset of symptoms of neuropathy. The bronchogenic carcinoma was anaplastic with local extension and metastasis, but no metastatic lesions were found in central or peripheral nerves. Striking histologic alterations were found in the posterior root ganglia: The ganglion cells were degenerated and replaced by the cap cells forming the residual nodules of Nageotte (Figure 4), and the posterior columns and the dorsal root distal to the ganglia were also demyelinated (Figure 5).

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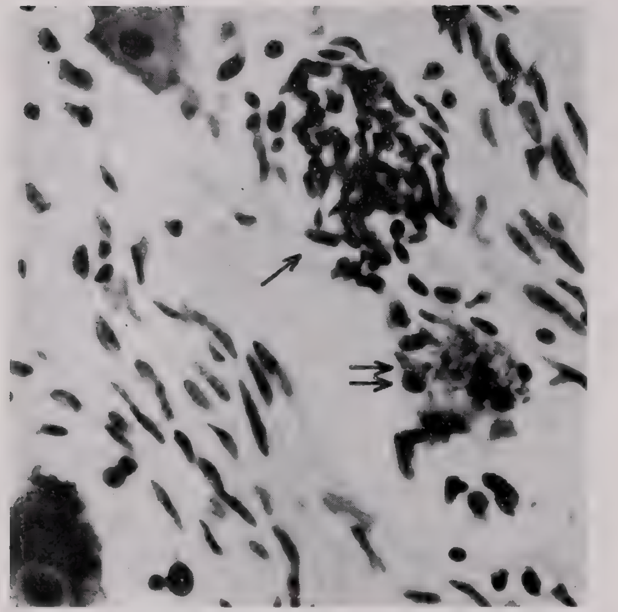

Fig. 4 — Dorsal root ganglia with residual nodules of Nageotte *(single arrow)* and early stages of neuronal degeneration *(pair of arrows)*. (Gomori iron stain, x120.) (From Dyck, P. J., Bailey, A. A., and Olszewski, Jerzy: Carcinomatous Neuromyopathy: A Case of Sensory Neuropathy and Myopathy with Onset Three and One-half Years Before Clinical Recognition of the Bronchogenic Carcinoma. Canad Med Ass J 79:915, 1958. By permission of the publisher, Canadian Medical Association Journal.)

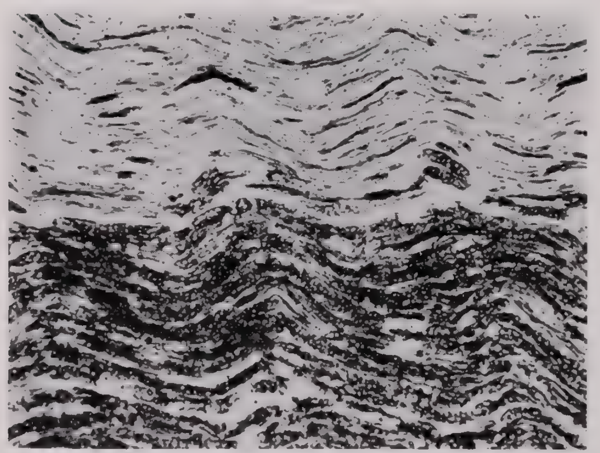

Fig. 5 — T3 spinal nerve just after the junction of fibers from the spinal ganglia, in upper half of picture, with the anterior root, in lower half of the picture. Note the demyelinization of the dorsal root fibers. (Heidenhain stain; x120.) (From Dyck, P. J., Bailey, A. A., and Olszewski, Jerzy: Carcinomatous Neuromyopathy: A Case of Sensory Neuropathy and Myopathy with Onset Three and One-half Years Before Clinical Recognition of the Bronchogenic Carcinoma. Canad Med Ass J 79:915, 1958. By permission of the publisher, Canadian Medical Association Journal.)

Denny-Brown[5] thought that the primary involvement in this condition is in the dorsal root ganglion and that the posterior column and sensory root demyelinization are secondary.

Carcinomatous Polio-Encephalopathy

A carcinomatous polio-encephalopathy has been described as being characterized by a rapid deterioration in memory, sometimes associated with cerebellar ataxia. In another group of cases the rapidly progressive cerebellar ataxia, sometimes associated with lesser mental changes and brain-stem and long-tract signs, is predominant. In still another group, the main changes are in the brain stem. In the cerebellar group the points which distinguish it from other causes of progressive cerebellar ataxia are: (1) the patient is older than the usual patient at the onset of multiple sclerosis, and (2) the progression of the disability is much more swift than is usually seen in degenerate cerebellar disorders.

Carcinomatous ALS

Norris and Engel[14] described a carcinomatous amyotrophic lateral sclerosis because they found a significant carcinoma in 10% of 130 consecutive cases of amyotrophic lateral sclerosis. However, Mulder[15] did not find any significant malignancy in the 100 consecutive patients with amyotrophic lateral sclerosis whom he saw in 1954 at the Mayo Clinic and whom he followed until their death (in all but a few cases). I have briefly reviewed the coded diagnosis in the first 200 consecutive cases (from 1949 to 1954) diagnosed as amyotrophic lateral sclerosis by the neurologists at the Mayo Clinic. Only two of these cases included recognized, significant tumors, and in both cases the tumors seemed to be unrelated to the amyotrophic lateral sclerosis in time, having been treated successfully and without evidence of recurrence — by radical mastectomy in one case and resection of sigmoid carcinoma with end-to-end anastomosis in the other — four years before the onset of symptoms of amyotrophic lateral sclerosis.

This striking difference in incidence of significant malignancy in patients with amyotrophic lateral sclerosis is hard to explain. It may be related in part to differences between the patients referred to the National Institutes of Health and the University of Rochester and those seen at the Mayo Clinic. Another difference may be in the criteria used to diagnose amyotrophic lateral sclerosis — for example, Case 2 of Norris and Engel would probably not have been included as an amyotrophic lateral sclerosis case at the Mayo Clinic. Finally, another difference may be in the criteria used for the diagnosis of significant malignancy; in Norris and Engel's Cases 7, 9, and 13 no evidence had been found of recurrence of an earlier malignant lesion in spite of intensive investigation, and in their Case 11 even postmorten examination did not disclose it. Therefore, the association between amyotrophic lateral sclerosis and significant malignancy does not seem to be a closed question.

Some difference of opinion also exists regarding the incidence of malignancy in polymyositis and dermatomyositis. Christiansen and co-workers[16] reviewed 270 cases of dermatomyositis at the Mayo Clinic and found approximately 7% with an associated malignancy. In a group of 104 patients with polymyositis or dermatomyositis, Mulder and co-workers[17] found an incidence of malignancy of almost 7%. In striking contrast to these data are those of Shy[18] who found an over-all incidence of carcinoma of 18 to 30% in myopathies of late onset. Among patients more than 50 years of age, the incidence was 39%. The association was even more striking in men, with carcinoma found in 71% of cases.

Mechanisms

Nutritional

Historically, it was thought that cachexia explained the neuropathy of carcinoma. As pointed out by Denny-Brown,[5] a posterior ganglion degeneration does occur in experimental animals deficient in pantothenic acid. However, administration of vitamin supplements to subsequent patients with carcinomatous sensory neuropathy was of no benefit. It is still possible that some of the neurological syndromes are the result of a deficiency of a vitamin, amino acid, or other essential biochemical factor.

Viral Infection

Another mechanism may be the coexistence of a viral infection — for example, herpes zoster infection in the lymphomas and possibly a glial virus in progressive multifocal leukoencephalopathy. Another explanation of the relationship between neurological syndrome and carcinoma might be the hypothesis that an environmental carcinogen produces both. Prehn[19] has argued that it is even possible that a carcinogen might release antigens which then precipitate auto-immune disease. Wilkinson[20] found organ-specific complement-fixing antibodies to antigens in unmyelinated dorsal roots and central nervous system gray matter in a case of carcinomatous sensory neuropathy. This then may be the counterpart of experimental allergic encephalitis and experimental allergic neuritis seen in the experimental animal.

Toxic Substance

There is also the possibility that the neurological symptoms are caused by a toxic substance produced by tumors. Recently, several cases have been described in which a tumor appeared to be responsible for the excretion of excessive amounts of porphyrins. Since marked central and peripheral nervous system derangements are associated with another well-known condition in which there is excessive porphyrin excretion — intermittent porphyria — this mechanism should be kept in mind. Finally, the medications and radiation treatments used may themselves be toxic to the normal nervous system.

Summary

This review lists and discusses some of the neurological disorders found to be associated with malignant lesions but not due to actual invasion of nerve tissue by tumor. The strongest case for a significant relationship between a neurological disorder and a ma-

Continued

lignant lesion occurs when the neurological state is distinctive and is always associated in time with one kind of malignant lesion. Three syndromes come close to fulfilling these criteria: sensory neuropathy, myasthenic syndrome, and progressive multifocal leukoencephalopathy. With polio-encephalopathy, polymyositis and dermatomyositis, and amyotrophic lateral sclerosis, the association with carcinoma is less striking. These neurological syndromes are most frequently seen unassociated with malignant lesions and, when associated with malignant lesions, the lesions may be of many types. Finally, the high incidence of carcinoma in patients with amyotrophic lateral sclerosis reported by Norris and Engel has not been confirmed in this report.

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Security

You cannot bring about prosperity by discouraging thrift. You cannot strengthen the weak by weakening the strong. You cannot help the earner by pulling down the wage payer. You cannot further the brotherhood of man by encouraging class hatred. You cannot help the poor by discouraging the rich. You cannot establish sound security on borrowed money. You cannot keep out of trouble by spending more than you earn. You cannot build character and courage by taking away man's initiative and independence. You cannot help men permanently by doing for them what they could and should do for themselves. — Abraham Lincoln

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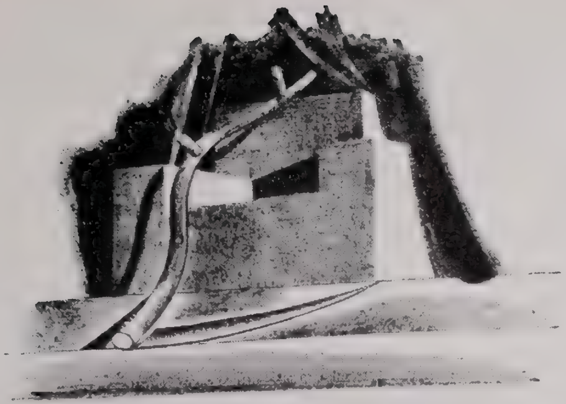
The only competition worthy of a wise man is with himself. — Washington Allston



In Memoriam

To neglect, at any time, preparation for death, is to sleep on our post at a siege; to omit it in old age, is to sleep at an attack. — Johnson

LEROY M. EKSTRAND, M.D.

Dr. Leroy M. Ekstrand, 50, member of the Wabasha Community Clinic staff, died August 17. He had practiced medicine in Wabasha since 1946. Born in Waukegan, Illinois, Dr. Ekstrand was a graduate of the University of Illinois School of Medicine.

He was a member of the Wabasha County Medical Society, American Medical Association, Minnesota State Medical Association, American Academy of General Practitioners and American Legion Post 50.

He is survived by his wife and five sons.

JOHN J. CATLIN, M.D.

Dr. John J. Catlin, 85, former Buffalo physician, died August 20 in Macomb, Illinois. Born in Delano, he obtained his medical degree at the University of Minnesota.

Dr. Catlin was a former officer of the Wright County Medical Society and a member of the American Medical Association. He was a life and 50 Club member of the Minnesota State Medical Association.

He is survived by his wife, four daughters and a son, Dr. Theodore J. Catlin of Buffalo.

S. MARX WHITE, M.D.

Dr. S. Marx White, 93, Minneapolis heart and tuberculosis specialist and public health official, died August 30. Born in Hokah, Minnesota, Dr. White received his medical degree at the Northwestern University Medical School in Chicago.

He came to the University of Minnesota as a pathology instructor in 1898 and after 44 years of teaching at the school, was made professor emeritus.

A cofounder of the Nicollet Clinic in Minneapolis, Dr. White had been a member of the Board of Regents of the American College of Physicians, serving as national president from 1931 to 1932. He founded and directed the Glen Lake Tuberculosis Sanatorium and had been director of the Hennepin County Tuberculosis Association. In 1951 he received the Distinguished Community Service Award of the Community Chest and an award from the Junior Chamber of Commerce.

He was a member of the Hennepin County Medical Society and American Medical Association and a life and 50 Club member of the Minnesota State Medical Association.

He is survived by two daughters and a son, Dr. Asher A. White of Minneapolis.

ALFRED T. BAKER, M.D.

Dr. Alfred T. Baker, 82, Minneapolis physician, died September 2. Born in Ida Grove, Iowa, he graduated from the Chicago College of Medicine and Surgery and received his B.S. and M.D. degrees from the University of Minnesota. Dr. Baker was one of the original six members of the closed staff of Eitel Hospital in Minneapolis. He also was a former chief-of-staff at Eitel Hospital.

He was a member of the Hennepin County Medical Society and American Medical Association and a life and 50 Club member of the Minnesota State Medical Association. In 1954 he retired from private practice because of illness.

He is survived by his wife and a daughter.

SYMPOSIUM ON ADOLESCENCE

NEW ORLEANS, LOUISIANA **DECEMBER 1-3, 1966**

Approved for 15 hours credit by the American Academy of General Practice
Sponsored by the
DIVISION OF PSYCHIATRY and COMMUNITY MENTAL HEALTH CENTER
OF TOURO INFIRMARY
supported by a National Institute of Mental Health Grant

GUEST LECTURERS INCLUDE:

Dana Farnsworth, M.D., Director of Student Health Services at Harvard University, Cambridge, Mass.
Irvin Kraft, M.D., Professor of Child Psychiatry at Baylor Medical School, Houston, Tex.
John Schimel, M.D., Associate Director of William Alanson White Institute of Psychiatry, Psychoanalysis and Psychology, New York, N. Y.
George Tarjan, M.D., Professor of Psychiatry and Program Director of Mental Retardation Project at University of California in Los Angeles, Calif.
Carroll Witten, M.D., President-Elect of American Academy of General Practice, Louisville, Ky.

AMONG TOPICS TO BE DISCUSSED:

"The Physician's Role in Mental Retardation"
"Parents of Problem Children"
"Handling of Adolescents by General Practitioners"
"Sexual Morality — A College Dilemma"
"Drugs in the Treatment of Children and Adolescents"
"Learning Problems of the Adolescent"
"Adolescence and Social Mores"
"Talking About Sex with Adolescents"
"Religious — Psychological Conflicts"

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Gene L. Usdin, M.D.
Director of Psychiatric Services
Touro Infirmary
1400 Foucher Street
New Orleans, Louisiana 70115

Enclosed is my registration fee of $20 for the SYMPOSIUM ON ADOLESCENCE to be given December 1-3, 1966 at the Fontainbleau Motor Hotel. (Checks should be made payable to Touro Infirmary.)

Name____________________

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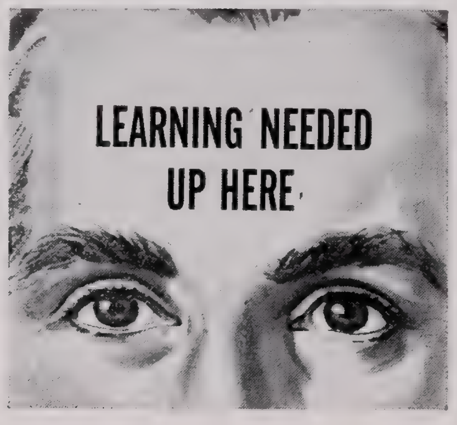

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Meetings and Announcements

To succeed in the world, it is much more necessary to possess the penetration to discern who is a fool, than to discover who is a clever man. — Talleyrand

OCTOBER

Minnesota Society of Internal Medicine, St. Paul — October 17, 8:00 a.m.

Blue Earth Valley Medical Society, Interlaken Golf Club, Fairmont— October 19.

Twin City Urological Society, Town & Country Club, St. Paul — October 21, 6:00 p.m.

Quain & Ramstad Fall Clinic Conference, Bismarck, North Dakota — October 22.

Ramsey County Medical Society — October 31, 8:00 p.m. regular meeting, 15th floor Lowry Medical Arts Bldg., St. Paul.

Southwestern Minnesota Medical Society, Worthington — October 3, 7:00 p.m.

Nicollet-LeSueur County Medical Society, Holiday House, St. Peter — October 3, 6:30 p.m.

Scott-Carver County Medical Society, Wagner's Colonial Club, Jordan, — October 4, 7:30 p.m.

Hennepin County Academy of General Practice, Pick-Nicollet, Minneapolis — October 6, 6:00 p.m.

Brown County Medical Society, Dakota Hotel, New Ulm — October 11, 7:00 p.m.

Minnesota Academy of Medicine, Town & Country Club, St. Paul — October 12, 6:30 p.m.

St. Louis County Medical Society, Ex. Comm. at 6:00 p.m., regular meeting at 8:00 p.m., October 13, St. Luke's Hospital, Duluth.

Camp Release District Medical Society, Hunt Hotel, Montevideo — October 13.

Hennepin County Academy of General Practice, Athletic Club, Minneapolis — October 17, 6:00 p.m.

American Society of Anesthesiologists — Sheraton Hotel, Philadelphia, October 1-5.

Clinical Orthopaedic Society — Chicago, Illinois, October 5-7.

American College of Surgeons — Fairmont Hotel, San Francisco, California, October 10-14.

Central Neuropsychiatric Association — Hilton Hotel, St. Paul, Minnesota, October 13-15.

NOVEMBER

Scott-Carver County Medical Society, November 1, Wagner's Colonial Club, Jordan, 7:30 p.m.

Zumbro Valley Medical Society, November 2 (Annual Meeting), Mann Hall, Mayo Clinic, 8:00 p.m.

Minnesota Society of Clinical Pathologists, November 5, Annual Tumor Seminar, Minnesota Club, St. Paul.

Hennepin County Academy of General Practice, November 7, Radisson Hotel, Minneapolis, 6:00 p.m.

Southwestern Minnesota Medical Society, November 7, Worthington, 7:00 p.m.

Minnesota Academy of Medicine, November 9, Town & Country Club, St. Paul, 6:30 p.m.

Camp Release District Medical Society, November 10, Hunt Hotel, Montevideo, 6:30 p.m.

St. Louis County Medical Society, November 10, Ex. Committee at 6:00 p.m.; regular meeting at 8:00 p.m., St. Mary's Hospital, Duluth.

Milwaukee Medical Conference, November 10-11, Milwaukee County Hospital, Milwaukee.

Minnesota Surgical Society, November 11, Scientific and business sessions, registration at 9:00 a.m., St. Paul-Ramsey Hospital, St. Paul.

Blue Earth Valley Medical Society, November 16, Interlaken Golf Club, Fairmont.

Minnesota Academy of Occupational Medicine and Surgery, November 17, Minneapolis Club, 6:30 p.m.

Twin City Urological Society, November 18, Town & County Club, St. Paul, 6:00 p.m.

Range Medical Society, November 22, Executive and general meeting, dinner at 7:00 p.m., meeting follows — either at Grand Rapids or Hibbing (not yet determined).

AMA Clinical Convention, November 27-30, Las Vegas.

Ramsey County Medical Society, November 28, 15th floor, Lowry Medical Arts Bldg., St. Paul, 8:00 p.m.

ANNOUNCEMENTS

Minnesota Obstetrical-Gynecological Society Meeting, December 3rd, Hennepin County General Hospital. Contact: Theodore Watson, M.D., 1261 Lowry Medical Arts Building, St. Paul.

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Contraindication: Not recommended during pregnancy.

Caution: May be habit-forming. Do not use in patients sensitive to barbiturates or in those with moderate to severe hepatic disease.

Side Effects: Nausea, transitory dizziness, rash. Overdosage of allobarbital produces symptoms typical of acute barbiturate excess.

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Partnership Life Insurance

Frequently the question arises in medical partnerships as to whether the purchase of a partner's interest upon his death should be funded by the purchase of insurance on the lives of the partners. Briefly, this is accomplished by a system of cross-insurance whereby a policy is carried on each partner's life. Each policy on a partner's life is owned by all the other partners who are also beneficiaries of that policy. For example, in the "A, B, C" partnership, "A" and "B" own a policy on "C"; "A" and "C" own a policy on "B"; and "B" and "C" own a policy on "A." Due to varying ages and rates, the insurance premiums are generally totaled and charged to the partners on an equal basis. These premiums represent personal nondeductible expense to the partners.

Since the policy on a partner's life is owned by the other partners, this insurance is not included in his estate in case of death. The proceeds of a policy, in case of death, are tax free to the beneficiary partners.

What are some of the advantages of such a plan?

1. It provides immediately available cash upon the death of a partner for liquidation of his capital interest.
2. It eliminates any risk of a partner's estate not getting its money from the remaining partners.
3. It eliminates any financial burden on the partners in the case of death of one or two members and it insures the continuation of the partnership. Often without such insurance, it is necessary to liquidate the partnership in order to pay off a deceased member's interest.

The major disadvantages are:

1. Each partner finances the liquidation of his own capital account indirectly by paying his pro rata share of the cost of the insurance. This benefits his partners but not his own family.
2. Advanced age and insurability often make the cost of such an insurance program extremely high.
3. For partners who are financially independent, this may represent an unnecessary expenditure.

What then is the best approach to determining whether or not a partnership should purchase life insurance on its members?

1. A determination should be made of just what the capital investment is in a partnership and whether or not this investment is adequate to necessitate an insurance program. In many manufacturing and retail firms the capital investment is extremely high and represents all the assets of the partners. This is not generally true of professional partnerships.
2. A review should be made of ages, insurability and financial status of each partner involved. This will reveal both the cost of an insurance plan and, combined with paragraph "1," the need for an insurance plan.
3. A study should be made of workable alternatives to an insurance plan. These include such things as available credit for financing (building, equipment, et cetera), payment of a partner's interest in accounts receivable as collected, and installment payments to an estate in settlement of the remaining capital interest.

As an example of a partnership insurance problem and its solution, let us consider the "A, B and C" partnership. These Doctors own an office building and equipment valued at $54,000 and have accounts receivable of $39,000. The per-man cost of liquidating would be $31,000 in the event of death. Doctor "A" is 57 years of age and independently wealthy. He has a physical condition that would increase his life insurance cost by 20%. Doctor "B" is 41 and could easily borrow funds to purchase his share of a partner's interest. Doctor "C" is 29 and has no resources whatsoever. His maximum credit would be about $5,000.

Here is the solution they chose. Accounts receivable were made self-liquidating; in case of death, they would be frozen and each partner paid his interest as they were collected. In their partnership agreement a clause provides that surviving partners have the option of paying off the deceased partner's interest, either in full or over a period of five years, with minimum payments of $300 per month at 5% interest. As added protection, each doctor has his own credit and resources and the surviving doctors also have a mortgagable building which could provide $25,000-$30,000 purchase money at 5½%.

In this case, we feel that their solution is much more workable than an extremely high-cost insurance plan. In summary, we feel that large life insurance programs *generally* are not necessary for professional partnerships and that the insurance premiums can be used by the doctors with less resources to provide much needed insurance protection for their own families.

Since this is only *generally true*, there are individual exceptions; therefore, an extensive individual study should be made by the partners, their attorneys and their financial advisers before a program of life insurance is adopted. Such a study will determine whether a need exists for partnership life insurance and, if so, how large a program is necessary.

William D. Huntington[*]
Minneapolis, Minnesota

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[*] Northern Division Manager, Professional Management Midwest.

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Classified advertising rates are twenty (20) cents a word; minimum monthly charge $5.00; key number, fifty (50) cents additional.

Replies to advertisements with key numbers should be mailed in care of MINNESOTA MEDICINE, *496 Lowry Medical Arts Bldg., St. Paul, Minn. 55102*

GENERAL PRACTITIONER wanted to join well-established practitioner. New clinic building — 90 miles east of St. Paul — city of 14,000. Early partnership with full hospital facilities. Ideal location. L. W. Picotte, M.D.; Chippewa Falls, Wisconsin.

GENERAL PRACTITIONER: Four-man group desperately needs fifth physician. 3,300 growing rural town with three good industries. 50-bed hospital with 50-bed nursing home attached. Salary first year then full partnership. Contact: R. W. Gustafson, M.D.; Granite Falls, Minnesota.

A THREE MAN GROUP needs a fourth general practitioner in a fast-growing West St. Paul area. Begin with salary and join partnership with full participating advantages. Write: MINNESOTA MEDICINE — 305, 496 Lowry Medical Arts Building, St. Paul 55102.

FOR SALE: Mattern x-ray unit K.V.-60. Good for chest and extremity work. Also an examining table, instrument cabinet, E.K.G., and other equipment. Contact L. A. Whitesell, Jr., M.D. 207 South 1st Street, Buffalo, Minnesota 55313.

EASTERN WISCONSIN CLINIC in rapidly growing community of 40,000 desires board-eligible or certified physicians in pediatrics, obstetrics and gynecology and internal medicine. Well-equipped clinic and excellent hospital facilities. Lake shore location offers ample recreational facilities. Attractive financial plan leading to early full partnership. Full expenses paid for applicants invited to interview. Call or write: F. L. Hildebrand, M.D., Riverside Clinic, Menasha, Wisconsin.

INTERNIST for 20-physician-clinic in prosperous Minnesota city. Salary negotiable first year, then full partnership. East Range Clinic, Virginia, Minnesota.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with early partnership. Write: MINNESOTA MEDICINE — 289; 496 Lowry Medical Arts Building; St. Paul, 55102.

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WANTED: young general practitioner to join six-man group consisting of 4 GPs, a general surgeon, and radiologist. College town of 22,000, 30 miles from Twin Cities. Also need LOCUM TENENS in general practice. Contact: Ed Jenkins, Mgr., River Falls Medical Clinic, River Falls, Wisc. Phone 425-5322.

WANTED — Internist, board certified or qualified, to associate with two board certified internists. Ten man multi-specialty group. (Lenont Peterson Clinic, Virginia, Minnesota) — Heart of the expanding taconite industry.

PSYCHIATRIC RESIDENCY POSITIONS AVAILABLE: July, 1967, for three year accredited program PRMP. A dynamically oriented broadly-based well-balanced opportunity for sound training. Meadowbrook Hospital is Nassau County General Hospital and is centrally located in the most desirable and beautiful area in the country. Easy commuting distance to New York City. 2800 inpatient psychiatric admissions per year. 24 hour walk-in clinic, and all psychiatric modalities. Abraham S. Lenzner, M.D., Director, Psychiatric Education, Meadowbrook Hospital, P.O. Box 175, East Meadow, Long Island, New York, 11554.

WANTED: Young internist and pediatrician, board certified or eligible, to join 6-man group consisting of 4 GP's, a general surgeon, and a radiologist. College town of 22,000 only 30 miles from Twin Cities. Salary open with early partnership opportunity. Write or call collect: Ed Jenkins, Mgr., River Falls Medical Clinic, River Falls, Wisc., phone 425-5322.

GENERAL PRACTITIONER, associate, urgently needed. Unopposed practice established 20 years. 32 bed new hospital with additional 20 bed chronic unit. Good anesthesia coverage, lab. facilities. Excellent clinic one block from hospital. Salary with early partnership. Locum tenens also considered. Call collect 218-782-4725 or write Klefstad Clinic, Greenbush, Minnesota.

WANTED: GP to join clinic serving population area of 12,000. City has new hospital, new clinic building, two nursing homes, new Jr-Sr high school, new swimming pool, rich farming area in Red River Valley. Fishing and hunting nearby; metropolitan city close by. Salary open and partnership if interested. Write or call Warren Clinic, Warren, Minnesota 742-6231, area code 218.

LARGE GROUP WITH OFFICES IN TWO CITIES is looking for General Practitioner to add to a two-man general practice clinic. Practice limited only by your abilities and interests with ready consultation from specialty partners in other office located in adjacent city. Full partnership after first year. Write: MINNESOTA MEDICINE — 358; 496 Lowry Medical Arts Building, St. Paul, 55102.

WANTED: PHYSICIAN to associate with two General Practitioners, 30 miles from Twin Cities, salary open, with early partnership. New clinic and hospital. Call 835-3129 or 835-2722, or write Doctors Clinic, Forest Lake, Minnesota.

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LOCUM TENENS for January and February or at least January 15 through February 15. Southeastern Minnesota. $1500 stipend per month. Write: MINNESOTA MEDICINE-363, 496 Lowry Medical Arts Bldg., St. Paul 55102.

AVAILABLE SOON: Fascinating General Practice Partnership for sale in pleasant central California community just two hours from the ocean on high Sierras. Gross over $160,000 although each partner off 30% of the time in the past six years. Excellent duck, pheasant and deer hunting nearby. Profitable hospital laboratory and X-ray service included. Office conveniently located in hospital with open staff. Homes available if desired. Also, lake and ski cabin in North Shore Lake Tahoe Area. Terms negotiable near fair value. Write: MINNESOTA MEDICINE — 362; 496 Lowry Medical Arts Building, St. Paul 55102.

WANTED: G.P. or Internist willing to do some G.P. Twin-towns totalling 12,000, Western Minnesota Group Now three G.P.'s and one FRCS surgeon. Modern clinic building with eleven assistants. X-ray and minor laboratory. 125-bed accredited hospital. Rotating calls one night a week and every fifth week-end. Hunting, fishing, golfing available. Initial salary $1500 per month. Opportunity for partnership in one or two years. Apply: C. W. Jacobson, M.D., Breckenridge, Minnesota.

GENERAL PRACTITIONER WANTED to associate with solo practitioner currently doing over $100 M annual volume. Guaranteed minimum salary, plus bonus. Central Minnesota Lake Region. Write: MINNESOTA MEDICINE-364, 496 Lowry Medical Arts Building, St. Paul 55102.

THREE MAN group in North West Wisconsin Resort, State Conservation and Retirement Area needs two more physicians adequately to serve their practice. Facilities offered are three-room physician suites, X-ray and lab under AMT technician, RN-only nursing personnel. New accredited thirty-two bed hospital and forty-six bed nursing home. Deer and duck hunting, fishing within five minutes of town. Internist most needed; generalists welcomed. Will meet any reasonable salary request. Partnership after one year. Write: MINNESOTA MEDICINE-365, 496 Lowry Medical Arts Building, St. Paul 55102.

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G. P., age 31, two years experience, married with family, would like to relocate, limiting practice to medicine and pediatrics. Write: MINNESOTA MEDICINE — 361; 496 Lowry Medical Arts Bldg., St. Paul 55102.

General practitioner Wanted — Present physician retiring due to illness. New office Building, Call or write Anton Pharmacy, 879 S. Smith Ave., W. St. Paul. Phone 222-5700.

FOR RENT: Space available for surgical subspecialists. Excellent location. Near Unity Hospital, 10 minutes from Mercy. Share space with General & Thoracic Surgeon and 2 interns. Call Mrs. Winkel — 560-1700, Fridley.

PATHOLOGIST — Certified by the American Board of Pathology. Desires location in the Twin Cities area, large or small hospital. Four years experience. All openings considered. Write: MINNESOTA MEDICINE-366, 496 Lowry Medical Arts Building, St. Paul 55102.

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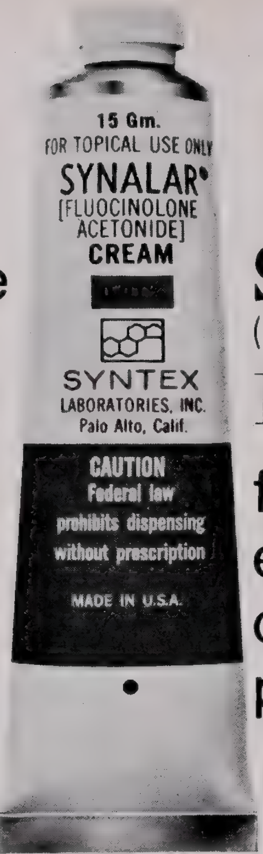

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Contraindications: Tuberculous, fungal, and most viral lesions of the skin (including herpes simplex, vaccinia, and varicella). Not for ophthalmic use. Contraindicated in individuals with a history of hypersensitivity to any of its components. **Precautions:** 1. *General*—Synalar Cream 0.01% is virtually nonsensitizing and nonirritating. Where severe local infection or systemic infection exists, the use of systemic antibiotics should be considered, based on susceptibility testing. While topical steroids have not been reported to
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relapses can be expected to occur in many psoriatic patients, remissi
may persist for several weeks to several months in favorable cases.
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Effects: Side effects are not ordinarily encountered with topically app
corticosteroids. As with all drugs, however, a few patients may react
vorably to Synalar under certain conditions. **References:** 1. Cahn, M. M.,
Levy, E. J.: J New Drugs 1:262 (Nov.-Dec.) 1961. 2. Meenan, F. O.: J
Med Ass 52:75 (Mar.) 1963. 3. Robinson, H. M., Jr., Raskin, J., and Duns
W. J. R.: Southern Med J 56:797 (Jul.) 1963.

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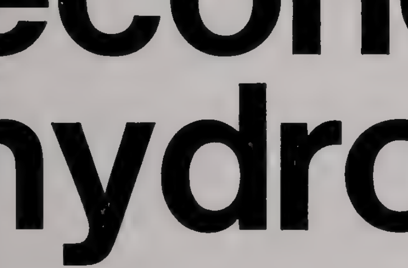
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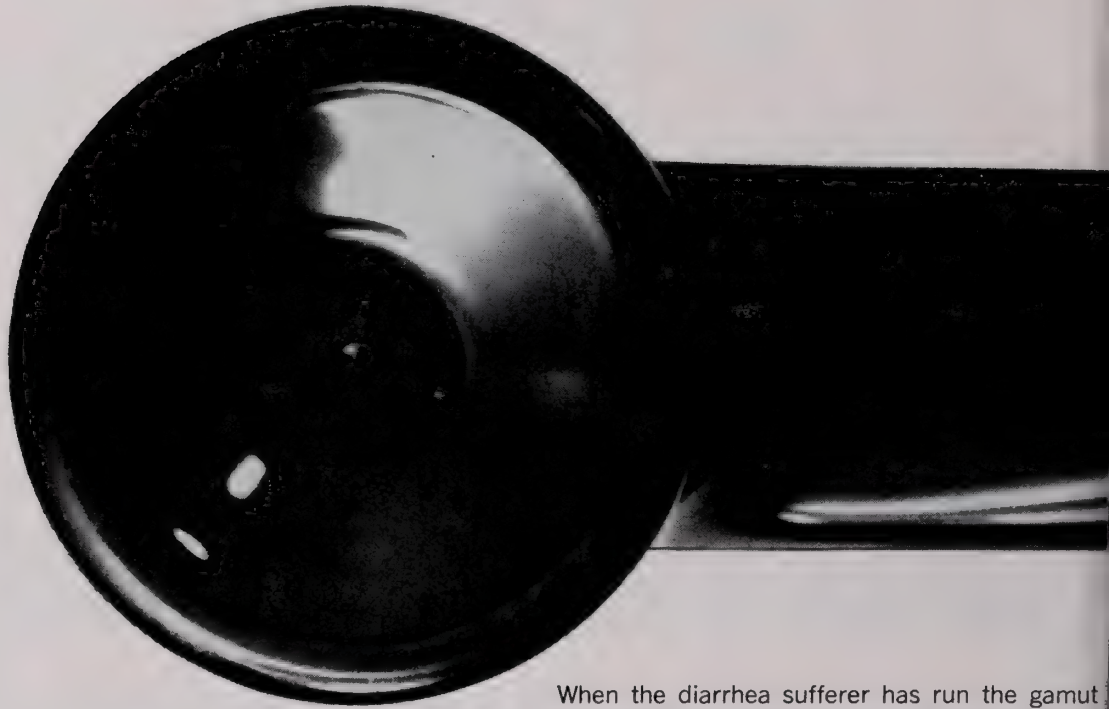

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CREMOMYCIN combines the bacteriostatic agen
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CONTRAINDICATIONS: Do not use in intestinal obstruction,
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to sulfonamides or neomycin; in pregnancy at term, in prema
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WARNINGS: Use only after critical appraisal in patients
hepatic or renal damage, urinary obstruction, or blood dys
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ported with use of sulfonamides. Consider periodic blood cou
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PRECAUTIONS: Succinylsulfathiazole: Use with caution if t
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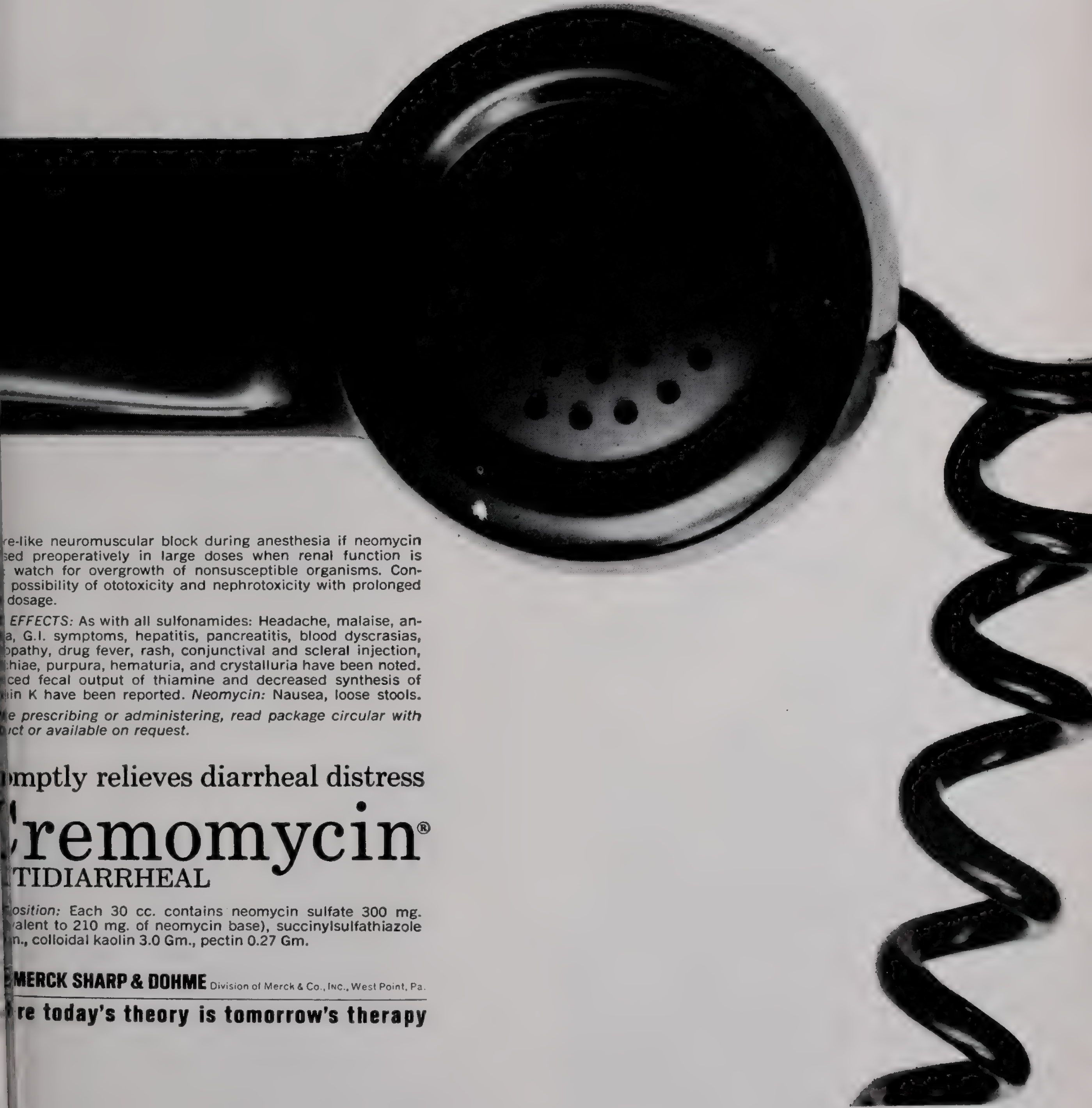

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And for your patient's sake, prescribe Alertonic in the convenient, economical one-pint bottle.

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Each 45 cc. (3 tablespoonfuls) contains: alcohol, 15%; pipradrol hydrochloride, 2 mg.; thiamine hydrochloride (vitamin B_1) (10 MDR[*]), 10 mg.; riboflavin (vitamin B_2) (4 MDR), 5 mg.; pyridoxine hydrochloride (vitamin B_6), 1 mg.; niacinamide (5 MDR), 50 mg.; choline,[†] 100 mg.; inositol,[†] 100 mg.; calcium glycerophosphate, 100 mg. (supplies 2% MDR for calcium and for phosphorus) and 1 mg. each of the following: cobalt (as chloride), manganese (as sulfate), magnesium (as acetate), zinc (as acetate), and molybdenum (as ammonium molybdate).

[*] Multiple of adult Minimum Daily Requirement supplied.

[†] The need for these substances in human nutrition has not been established.

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Dosage: Adults, 1 tablespoonful; children (over 15 years old), 1 to 2 teaspoonfuls; children (4 to 15 years old), 1 teaspoonful. To be taken three times daily 30 minutes before meals.

Contraindications: As with other drugs with CNS stimulating action, Alertonic is contraindicated in hyperactive, agitated or severely anxious patients and in chorea or obsessive compulsive states.

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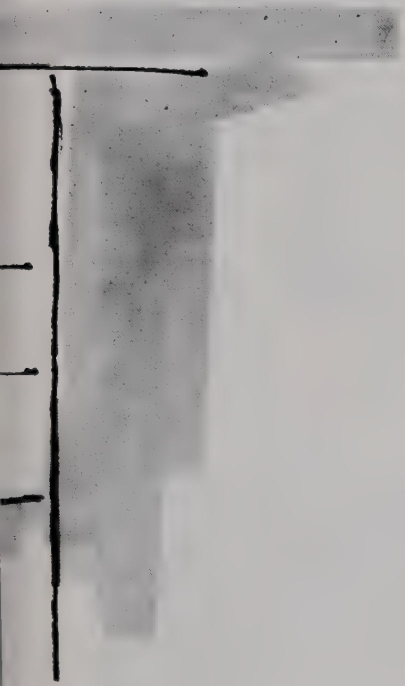

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Indications: Chronic and acute rheumatoid arthritis, rheumatoid (ankylosing) spondylitis, degenerative joint disease (osteoarthritis) of the hip, and gout.
Contraindications: Active peptic ulcer, gastritis, regional enteritis, or ulcerative colitis. Safety in pregnancy has not been established. Not recommended for pediatric age groups.
Warning: Patients who experience dizziness, lightheadedness, or feelings of detachment on INDOCIN should be cautioned against operating motor vehicles, machinery, climbing ladders, etc. Use cautiously in patients with psychiatric disturbances, epilepsy, or parkinsonism.
Precautions and Adverse Reactions: Most commonly, headache, dizziness, lightheadedness, G.I. disturbances. The C.N.S. effects are often transient and frequently disappear with continued treatment or reduced dosage. The severity of these effects may occasionally require cessation of therapy. G.I. effects may be minimized by giving the drug with food or with antacids or immediately after meals. Ulceration of the stomach, duodenum, or small intestine has been reported and, in a few instances, severe bleeding with perforation and death. Gastrointestinal bleeding with no obvious ulcer formation has also been noted; INDOCIN should be discontinued if G.I. bleeding occurs. As a result of G.I. bleeding, some patients may manifest anemia, and for this reason periodic hemoglobin determinations are recommended. Rare reports of effects not definitely known to be attributable to INDOCIN include bleeding from the sigmoid colon (either from a diverticulum or without a known previous pathologic condition), perforation of preexisting sigmoid lesions (diverticulum, carcinoma), and hematuria. In other rare cases, a diagnosis of gastritis has been made while the drug was being given. One patient developed ulcerative colitis, and another, regional ileitis, while receiving INDOCIN; when the drug was given to patients with preexisting ulcerative colitis, there was an increase in abdominal pain. Infrequently observed side effects may include drowsiness, tinnitus, mental confusion, depression and other psychic disturbances, blurred vision, stomatitis, pruritus, edema, and hypersensitivity reactions. Slight BUN elevation, usually transient, has been seen in some patients, although the preponderance of evidence indicates that INDOCIN does not adversely affect renal function, even in patients with preexisting renal disease. Nevertheless, renal function should be checked periodically in patients on long-term therapy. Leukopenia has been seen in a few patients. Transient elevations in alkaline phosphatase, cephalin-cholesterol flocculation, and thymol turbidity tests have been observed in some patients and, rarely, elevations of SGOT values; the relationship of these changes to the drug, if any, has not been established. As with any new drug, patients should be followed carefully to detect unusual manifestations of drug sensitivity. Before prescribing or administering, read product circular with package or available on request.

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1. Schleif, R.H.: J.A.PH.A., 46:179,1957 *U.S. Pat. No. 3,062,714

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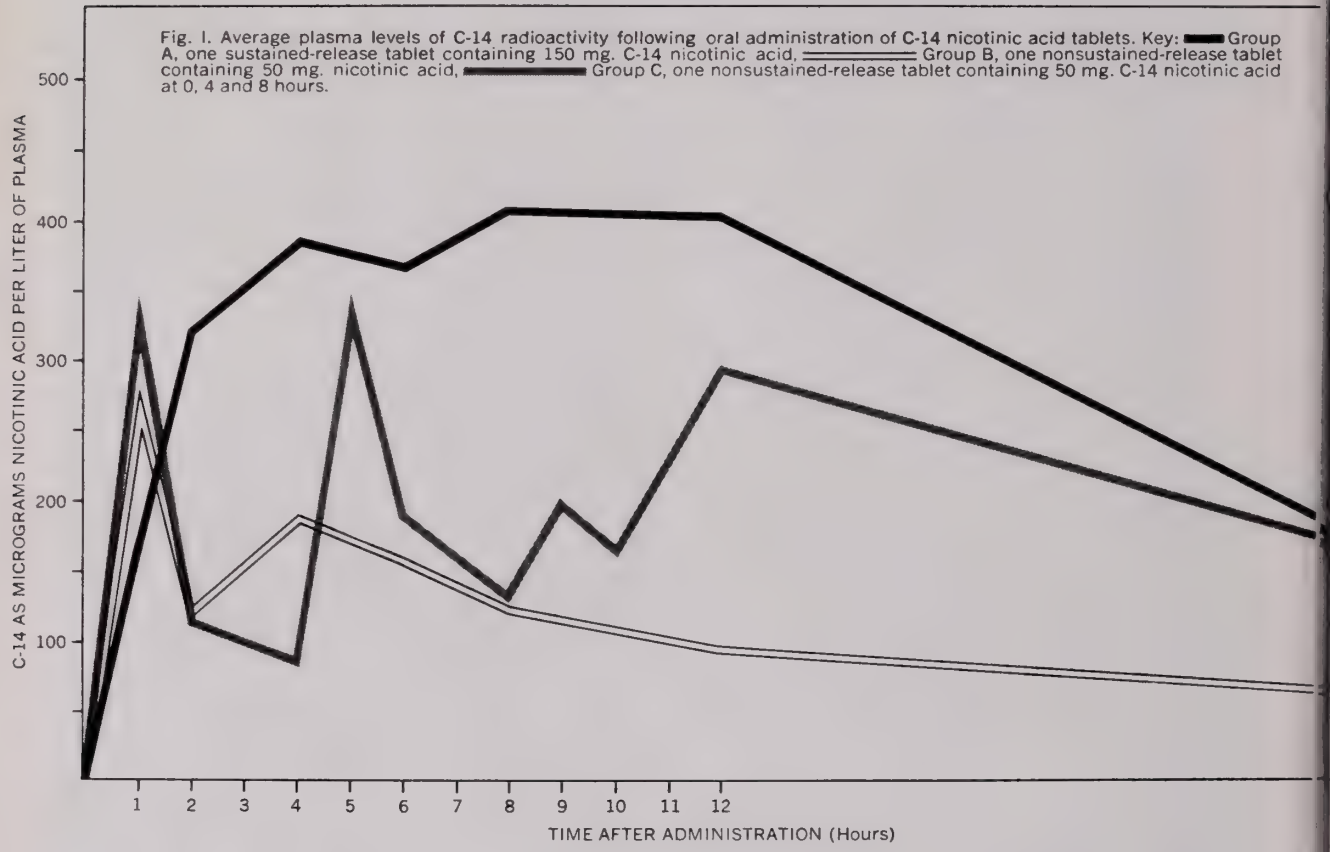

Fig. I. Average plasma levels of C-14 radioactivity following oral administration of C-14 nicotinic acid tablets. Key: ▬ Group A, one sustained-release tablet containing 150 mg. C-14 nicotinic acid, ═ Group B, one nonsustained-release tablet containing 50 mg. nicotinic acid, ▬ Group C, one nonsustained-release tablet containing 50 mg. C-14 nicotinic acid at 0, 4 and 8 hours.

(fewer absent doses by absent-minded patients

Human volunteer subjects were administered Geroniazol TT tablets with the nicotinic acid component made radioactive with C-14. Plasma and urine samples were analyzed. (See Figures I and II) The radioactive tracer study substantiated the previous clinical evidence that the release of nicotinic acid from the Geroniazol TT tablet produced a gradual rise in plasma levels to a plateau for a total of 12 hours and more.

Such proven sustained activity makes the management of geriatric patients much easier by minimizing the possibility of neglected doses through absent-

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let every 12 hours.

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TT will provide the well-known peripheral vasodi
tion needed in patients with deficient circulatior
with a minimum amount (if any) of "flushing."
cerebrovascular circulation is complemented by
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piratory stimulant.

Geroniazol TT improves the typical, unfortu
signs of senile confusion. Patients become more

ged and debilitated

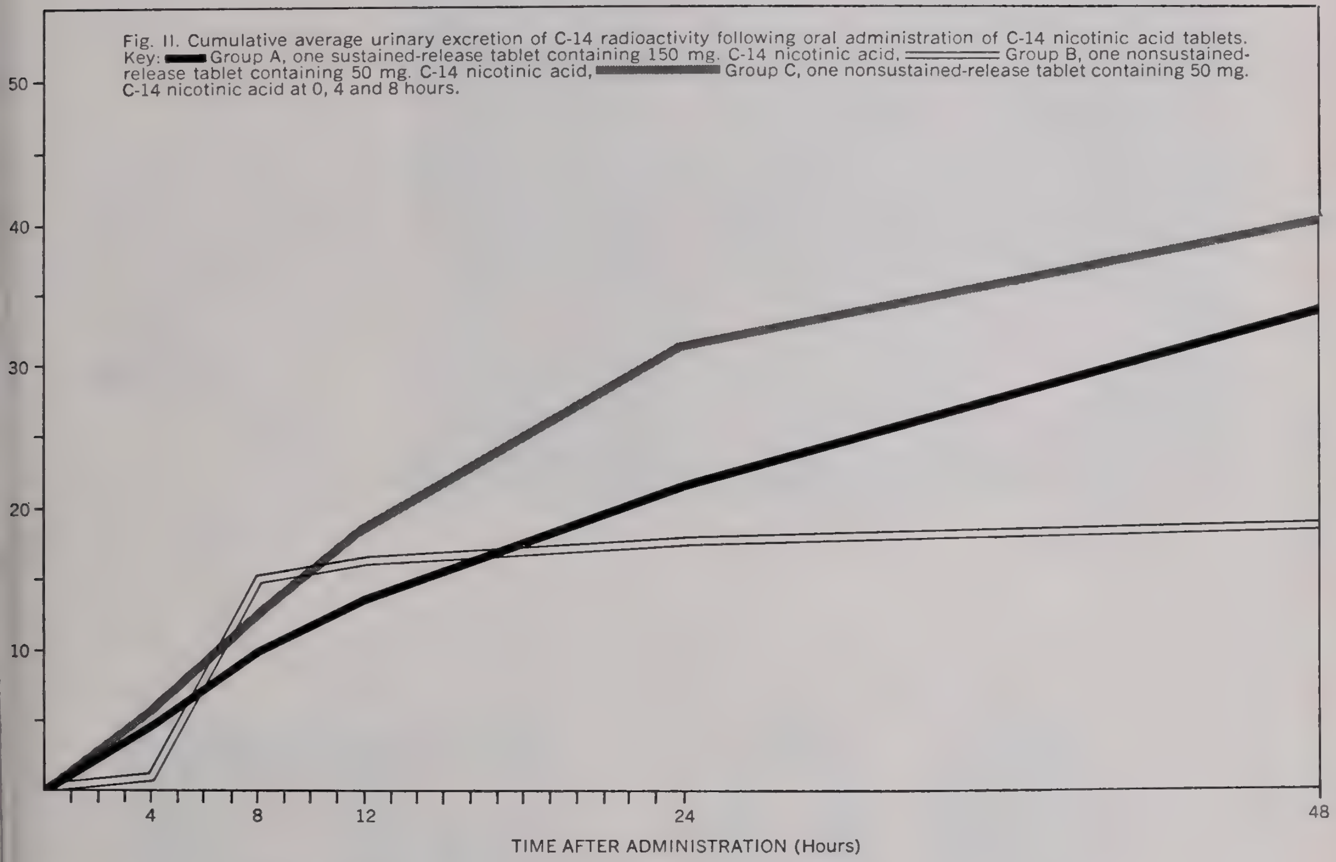

Fig. II. Cumulative average urinary excretion of C-14 radioactivity following oral administration of C-14 nicotinic acid tablets. Key: ▬ Group A, one sustained-release tablet containing 150 mg. C-14 nicotinic acid, ═ Group B, one nonsustained-release tablet containing 50 mg. C-14 nicotinic acid, ▬ Group C, one nonsustained-release tablet containing 50 mg. C-14 nicotinic acid at 0, 4 and 8 hours.

s confused and moody. Personal care, memory, otional stability, social attention improve. Fatigue, athy and irritability are reduced.

A prescription for 100 tablets of Geroniazol TT will rmit your patients to enjoy the benefits of time-olonged nicotinic acid/pentylenetetrazol therapy, an economical price. Dosage is only one tablet every hours.

ntraindications: There are no known contraindica-ns.

ecautions: Exercise caution when treating patients h a low convulsive threshold.

Side Effects: Side effects are rarely encountered, however due to the vasodilatation effect of nicotinic acid, transitory mild nausea, flushing, tingling and pruritus are possible.

Dosage: One tablet every 12 hours.

Supplied: Prescribe bottles of 100 tablets, to take advantage of recent price reduction.

References: 1. Report by Nuclear Science & Engineering Corp., Pittsburgh, Pa., in files of Philips Roxane Laboratories. 2. Connolly, R.: W. Virginia Med. J. *56*:263 (Aug.) 1960. 3. Curran, T. R., and Phelps, D. K.: Am. Pract. & Digest Treat. *11*:617 (July) 1960.

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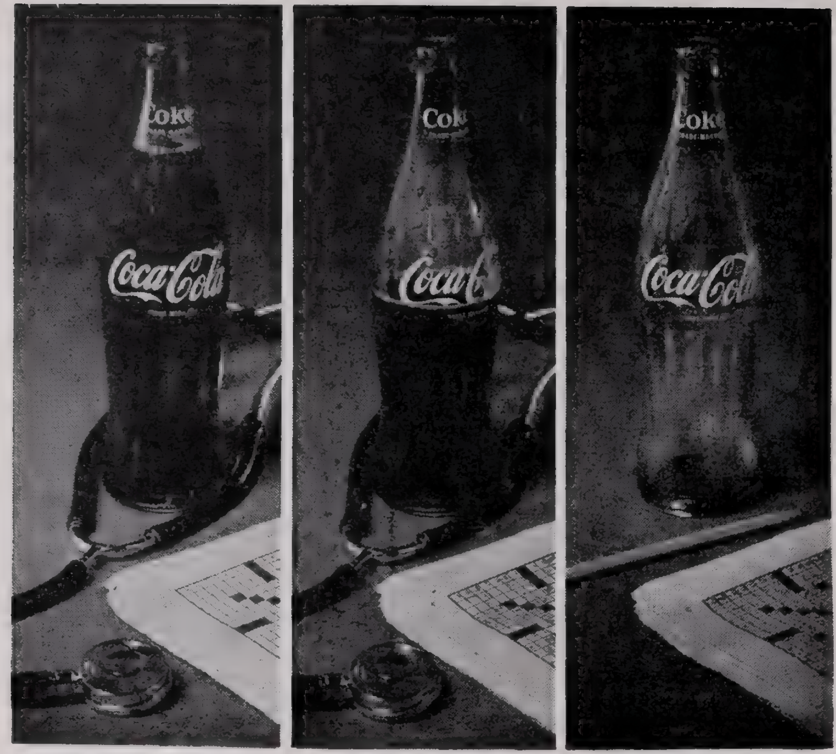

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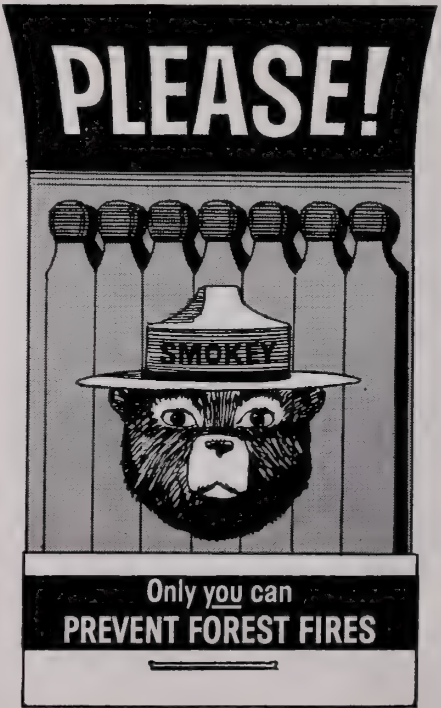

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Minnesota Medicine at a Glance

Surface Area and Dosage — Snively Page 1521

During the past century an increasing body of evidence has indicated that body surface area is directly related to such fundamental physiologic matters as heat production, cardiac output, glomerular filtration rate, blood pressure, organ size, oxygen consumption, nitrogen requirement, and plasma volume. It therefore appears to be our best gauge for dosage — far superior to age and to height, especially in the case of infants and children.

Until recently, determination of body surface area was a cumbersome matter. Now it can be done by the use of a simple chart from which one can read off body surface if he knows the weight. It can be similarly determined by the measurement of sitting height.

Authoritatively endorsed by the publication of the A.M.A. — *New Drugs;* by leading pediatric textbooks; by the National Formulary, and by an increasing number of teachers, it appears that body surface area will soon displace age and weight as a gauge for pediatric dosage. The rationale for body surface area and the simplicity of its application are explained in the article.

Surgical Treatment of Dizziness — Pulec Page 1529

The operation for continuous drainage of the endolymph fluid by a subarachnoid shunt, as described by Dr. Pulec, offers great promise for effective treatment of Meniere's disease in the relief of vertigo and preservation of hearing.

Left Ventricular Outflow — Karnegis and Wang Page 1545

Obstruction to the flow of blood from the left ventricle can occur at the aortic valve, above it, or below it. These all produce a pressure gradient which can be recorded by catheterization. As there are subtle differences among these conditions, definitive diagnosis can best be established by a cardiac catheterization or angiography.

Low Serum Cholesterol — Hunter Page 1555

Through the statistical evaluation and a determination of the factor of relative significance, Hunter has pointed out the importance of being cognizant of a low serum cholesterol level, as observed in a study of 750 patients. Though the incidence of low serum cholesterol is not high in any disease, it would seem to lend additional diagnostic value in those diseases in which Hunter has found it to be a factor of relative significance.

A review of this manuscript for both the positive and negative value is worth while.

Neurological Changes in Systemic Malignancy — Dyck Page 1629

Dr. Dyck reviews the expanding literature regarding a variety of neurological syndromes thought to be associated with systemic malignancies. These syndromes do not seem to be caused by actual invasion of the central or peripheral nervous system by metastatic lesions. Three syndromes are described in which a reasonably strong case can be made for a greater than chance relationship between malignancy and the neurologic syndrome. These include sensory neuropathy, myasthenic syndrome, and progressive multi-focal leukoencephalopathy. Other syndromes are discussed and some discrepancies between Mayo Clinic experience and other reported statistics are noted. A timely review of a little-known but important neurological problem.

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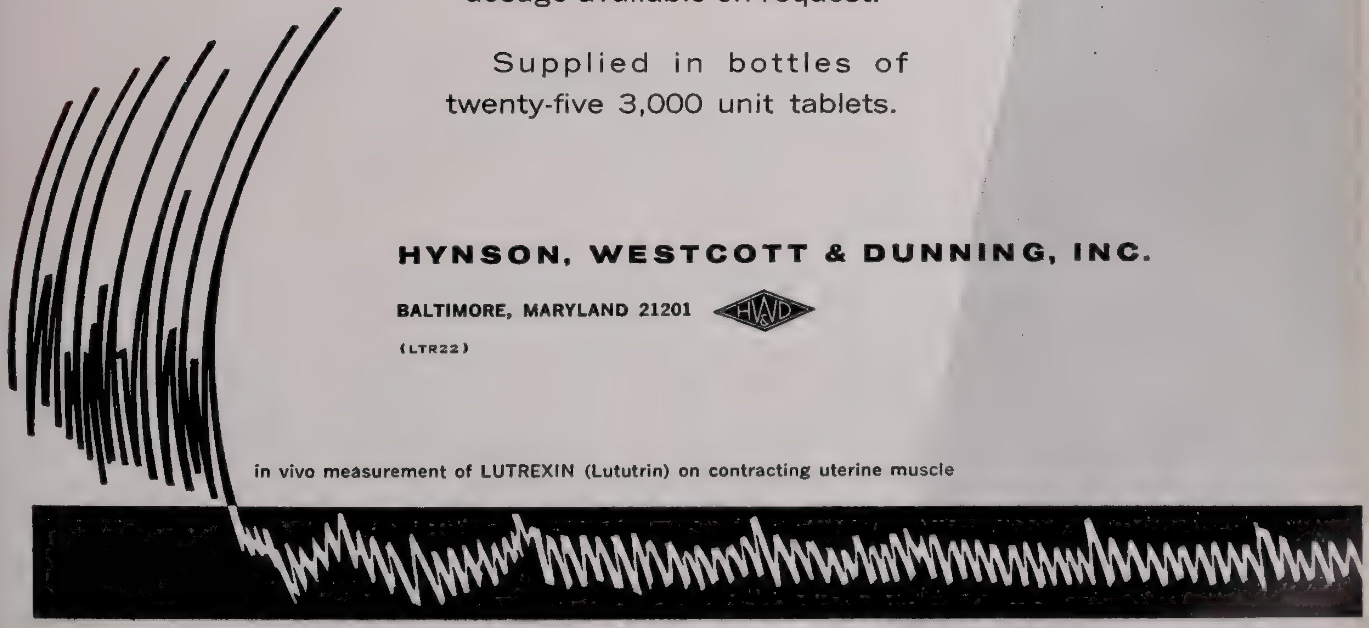

in vivo measurement of LUTREXIN (Lututrin) on contracting uterine muscle

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Precautions: As with all new drugs, blood and liver function tests are advisable during prolonged treatment. **Pending further experience, like most chemotherapeutic agents, this drug should not be given in the first trimester of pregnancy. It must be used cautiously in patients with liver disease or severe impairment of kidney function.** Because photosensitivity reactions have occurred in a small number of cases, patients should be cautioned to avoid unnecessary exposure to direct sunlight while receiving NegGram, and if a reaction occurs, therapy should be discontinued. The dosage recommended for adults and children should not arbitrarily be doubled unless under the careful supervision of a physician. Bacterial resistance may develop.

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President's Letter

THREE INQUIRIES — national, regional and local — into the training, the post-graduate education, and the distribution of physicians have involved the University of Minnesota Medical School, the Legislature of the State of Minnesota, and all physicians in a growing problem.

With publication of the study of the Health Manpower, the regional and state aspects of physician education supply and distribution are being clarified. The Hill Study is complete, and its conclusions and recommendations are published. The Legislative Sub-committee is still deliberating after meetings with representative physicians and other responsible medical organizations.

The third inquiry, commissioned by the American Medical Association became public in early October of this year.

The obvious conclusion drawn from these three inquiries is recognition of the national extent of the problem being considered in Minnesota at present on a state and regional basis.

The graduation of more physicians in Minnesota, the possibility of expanding our present medical school, the acceptance of more applicants from adjoining two-year schools, the development of a new medical school in Minnesota, an increase in number and change of format in medical school courses for generalists are the local proposals for meeting the national need for more physicians.

The provision for medical care to an expanding population, grown more sophisticated in demanding such care as a result of Federal programs, the expansion of prepaid group and individual plans, and rising personal incomes are responsibilities which medicine itself must recognize and assume.

Parallel situations exist in every phase of American life, education, paramedical technology, dentistry and the rest. Parallel efforts are being made to decrease shortages and improve distribution.

That the American Medical Association concerned with the twin-problem of medical education and physician availibility chose to go outside medicine by the appointment of the Citizens Committee indicates recognition of the value of non-involved opinion.

The same technique used in a somewhat different field of approach, in the Hill report, gave a depth to conclusions and recommendations which would have been more difficult to arrive at by a physician-dominated committee.

Ultimately, the effect of physician shortages in all areas of practice will be advanced by industry, by communities, by insurance carriers, and by those involved in the development of the resources of our State.

The solution will involve every citizen of Minnesota, and Medicine will do well to consider this in offering opinions and suggesting changes sound in concept and capable of execution.

R P Buckley M.D.

R. P. Buckley, M.D.
President
Minnesota State Medical Association

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Extracranial Internal Carotid Artery*

Surgery
for the
Occluded
Totally

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SINCE EASTCOTT, PICKERING and Rob[6] performed successful arterial resection and primary anastomosis for extracranial carotid artery stenosis in 1954, many reports support the surgical method of treating strokes in carefully studied and selected cases. The magnitude of the problem of cerebrovascular insufficiency, ranked as the third killer in the United States and responsible for 197,590 deaths in 1962, warrants a careful analysis of the results of treatment.

Under special consideration in this manuscript is a group of patients with total occlusion of the extracranial internal carotid artery. Are these patients candidates for surgery? Can the circulation be restored? Is there a sharp limitation in time from the onset of occlusion to the time of successful surgery? Discouraging reports can be found in the literature, most indicating that surgical efforts are unrewarding. Our personal experiences with this problem differ, indicating that in a substantial number of these patients, restoration of circulation can be accomplished as long as three weeks following the onset of total arterial occlusion.

Material

From the period March 2, 1958, to July 10, 1965, extracranial arterial disease producing cerebrovascular insufficiency was encountered in 140 patients. Twenty-four persons had bilateral carotid disease requiring operation. Of the 140 patients, 102 had internal carotid stenosis and 28 had total internal carotid occlusion. Total internal carotid artery occlusion thus occurred in 20% of the entire group. These and other lesions encountered are shown in Table 1. Our previous report[19] analysed the first 50 of these cases. The results of this continuing experience have been comparably encouraging, 82% of patients being improved or symptom-free after surgery.

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*Presented at the meeting of the Minnesota Surgical Society, Minneapolis, Minnesota, May 17, 1965.

See editorial page 1719.

Total Occlusion of Internal Carotid Artery

Twenty-eight of 140 patients had total occlusion of the extracranial internal carotid artery demonstrated by arteriography, percutaneous direct carotid injection, or by retrograde methods. Twenty-seven were operated. Fifteen of the 24 patients had bilateral arteriograms or aortic arch studies. Ten of these had bilateral disease, eight of whom underwent bilateral surgery. One patient had bilateral total occlusion of the internal carotid arteries.

Age and Sex

Ages ranged from 43 to 73 years. Seven of the 28 patients were less than 50 years. Twenty-four were males and four were females.

Symptoms

Sensory, motor, and visual disturbances were transient in 20 and persistent in eight of the 28 patients. Headaches, lightheadedness, dizziness, and fainting were also among the symptoms of some patients.

Interval from Onset of Total Occlusion to Time of Surgery

The time of total occlusion of the internal carotid artery was identified with the last preceding transient or persistent stroke prior to arteriography. Among 12 cases in which circulation was restored, intervals varied from eight hours to 21 days. In one instance (Case 23), transient symptoms commenced three months prior to arteriography and were not sufficiently separated to permit an accurate determination of the time of total occlusion (Table 2).

Among 15 patients in whom circulation was not restored by surgery, the onset of total occlusion was indeterminate in six. In the remaining nine, intervals varied from seven to 28 days (Table 3).

Operative Technique

All patients were operated under general anesthesia, and the methods for endarterectomy with and without patch grafting previously described were employed.[19] Intraluminal shunts were used occasionally to aid in arterial repair. In three cases heparin was administered in the preoperative period pending surgery. Heparin (50-75 mgm.) was employed prior to carotid artery clamping and was neutralized with protamine following endarterectomy and arterial repair.

Four times Fogarty balloon catheters[9] have been used in extracting soft clots, and in three instances retrograde flow was estab-

TABLE 1
Extracranial Arterial Stenosis and Occlusions

	Patients	Operations
A. Internal Carotid Artery Stenosis	102	125*
B. Internal Carotid Artery Occlusion	28	28**
C. Common Carotid Artery Occlusion	5	5
D. Vertebral Stenosis	4	4
E. Subclavian Stenosis	1	1†
	140	163

*23 patients had bilateral disease requiring surgery.
**One bilateral total occlusion.
†Producing subclavian steal syndrome.

TABLE 2
Interval From Time of Total Occlusion of Internal Carotid Artery to Time of Surgery
Twelve Successful Cases

Case 3	36 Hours
7	21 Days
9	18 Days
11	13 Days
13	6 Days
15	8 Hours
20	9 Hours
22	11 Hours
23	3 Months
24	9 Days
25	9 Days
28	19 Days

TABLE 3
Interval From Time of Total Occlusion of Internal Carotid Artery to Time of Surgery
Fifteen Unsuccessful Cases

Case 1	Indeterminate
2	Indeterminate
4	21 Days
5	17 Days
6	10 Days
8	10 Days-Not Operated
10	21 Days
12	Indeterminate
14	Indeterminate
16	Indeterminate
17	21 Days
18	7 Days
19	Indeterminate
21	28 Days
26	36 Hours
27	12 Days

lished after all other maneuvers such as forceps extraction and catheter suctioning had failed (Figure 3).

Pathology

In 25 cases there was chronic arteriosclerotic, partial occlusion with a superimposed recent thrombus (Figure 1) producing the total occlusion. In two cases, there was recent thrombosis of the internal carotid artery without significant arteriosclerosis at the carotid bifurcation. In these cases, it was felt that the occlusive process initiated intracranially and propagated extracranially.

Anatomical and Operative Results

Retrograde flow was established and the circulation was successfully restored in 12 of 27 patients operated or 12 of 28 arteries explored, one patient having total occlusion of both internal carotid arteries. Operative arteriograms were done in seven instances demonstrating arterial reconstruction and restoration of the intracranial circulation (Figures 2, 3, 4). In four instances arteriograms at seven days, eight days, six months, and 12 months postoperatively showed continued patency of the operated vessels.

There was one operative death in a 47-year-old man operated in a comatose state 36 hours after the onset of stroke. Despite a simple and expeditious endarterectomy, he died 40 hours later, never regaining consciousness. Autopsy was not performed.

Functional Results

Follow-up studies in eleven of twelve surviving patients in whom circulation was restored, classified according to Gurdjian,[11] show that seven are working and four are walking, one to 25 months following surgery. Among 13 patients followed in whom circu-

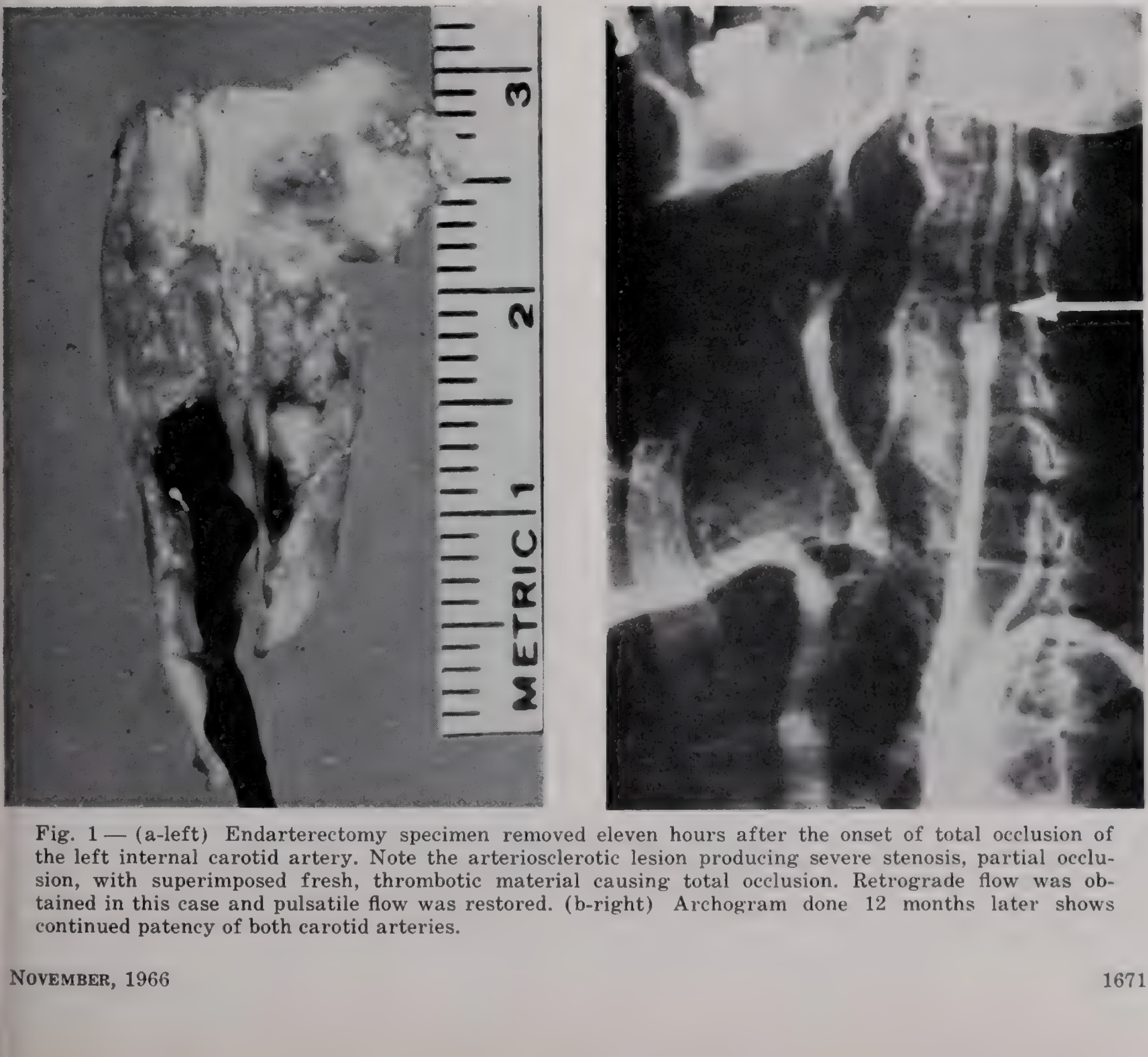

Fig. 1 — (a-left) Endarterectomy specimen removed eleven hours after the onset of total occlusion of the left internal carotid artery. Note the arteriosclerotic lesion producing severe stenosis, partial occlusion, with superimposed fresh, thrombotic material causing total occlusion. Retrograde flow was obtained in this case and pulsatile flow was restored. (b-right) Archogram done 12 months later shows continued patency of both carotid arteries.

lation was not restored, one died, four are working, four are walking, and four are wheel-chair patients.

The vagaries in following the functional aspects of surgery are well demonstrated in one of our patients, a 48-year-old man with intermittent right-sided strokes of three weeks' duration. On the day of hospitalization he became aphasic and developed a right hemiplegia. An archogram showed total occlusion of both internal carotid arteries and stenosis of one vertebral artery. Surgical exploration of both carotid arteries the same day disclosed old, chronic occlusion of the right internal carotid artery which was cordlike. The left internal carotid artery showed an atherosclerotic stenosis with a superimposed thrombus extending centrally. Circulation was not restored in either vessel. His prognosis was considered hopeless. However, with diligent and continuous nursing care by his wife, he survived, regained function of his paralysed side and began to phonate again. Continued evaluation of these results is necessary.

Discussion

Increasing recognition of extracranial vascular occlusions as the basis of strokes has led to more frequent use of arteriographic techniques for clarification of diagnosis and method of management.

In well selected cases of significant extracranial arterial stenosis, surgical procedures relieving the stenosis appear to be well established and uniformly good results can be expected in the majority of patients so treated. Admittedly, the functional results are more difficult to evaluate than the anatomical corrections made, and long-term studies are necessary for further elucidation.

Conflicting and contradictory views are found in the literature relating to the management of the totally occluded extracranial internal carotid artery. Thompson and Austin,[21] although restoring flow in 14 or 34 completely occluded internal carotid arteries, duration of occlusion not established, recommended exploration in acute occlusions of short duration, preferably hours, and in those in whom the arteriogram showed a pa-

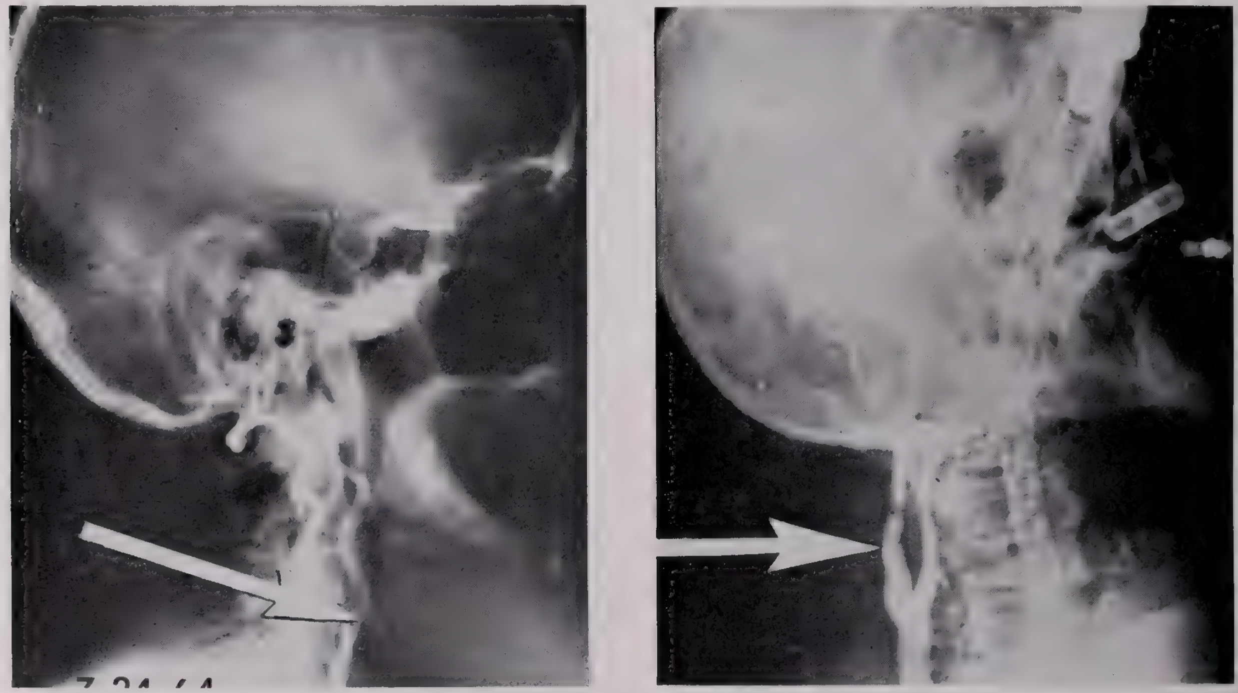

Fig. 2 — Case Nine: Duration of total occlusion on basis of history in this case was 18 days. (a-left) Preoperative arteriogram showing total occlusion of the internal carotid artery and absence of filling of the intracranial circulation. (b-right) Operative arteriogram following endarterectomy, thrombectomy, and arterial reconstruction. Flow has been re-established in the extracranial internal carotid artery, and the intracranial circulation is now evident. Revision of arteriotomy site shows improved caliber of internal carotid artery.

tent distal artery. Young and associates,[26] unable to restore flow in 14 patients with complete occlusions of greater duration than 24 hours, no longer operate these patients. Harrison[16] stated that the prospects of opening a totally occluded carotid artery after 24 to 48 hours are nil.

DeBakey[3] concurred with early intervention in the problem of total occlusion and previously reported[4] that complete occlusions were rarely operable unless explored soon after onset of symptoms. In a more recent report,[5] successful operation of a completely obstructed internal carotid artery was done in a patient with progressive neurologic manifestations of three months' duration.

Javid[18] stated that complete occlusion of the internal carotid artery is not an operable lesion, being unsuccessful in seven explorations. Cooley[2] advised exploration only in the acute occlusions because of the low success rate in restoring circulation in the chronically occluded cases. Ellis,[8] too, held little chance for restoring circulation unless the occlusion was of relatively recent origin. Whisnant[22] and associates again supported this stand. Wisiol[23] reported poor results with total arterial occlusions, as did Bahnson,[1] Murphey,[20] Edwards,[7] and Haller.[14]

TABLE 4
Total Occlusion Internal Carotid Artery Operative Results
Twelve Successful Cases

	Back-Flow Restored	Arteriograms
Case 3	+	Not Done
7	+	+
9	+	+
11	+	Not Done
13	+	+
15	+	Not Done
20	+	Not Done
22	+	+
23	+	Not Done
24	+	+
25	+	+
28	+	+
	12	7

Gunning[10] reported restoration of flow in five of 15 totally occluded arteries, three of which subsequently thrombosed. Hardin[15] reported ten cases of completely occluded internal carotid arteries, four of which died following surgery, apparently in progressive stroke. Hohf[17] reported six of 12 totally occluded arteries patent six months after operation. The duration of total occlusion was not given.

In Gurdjian's extensive experience with the overall problem of carotid artery occlu-

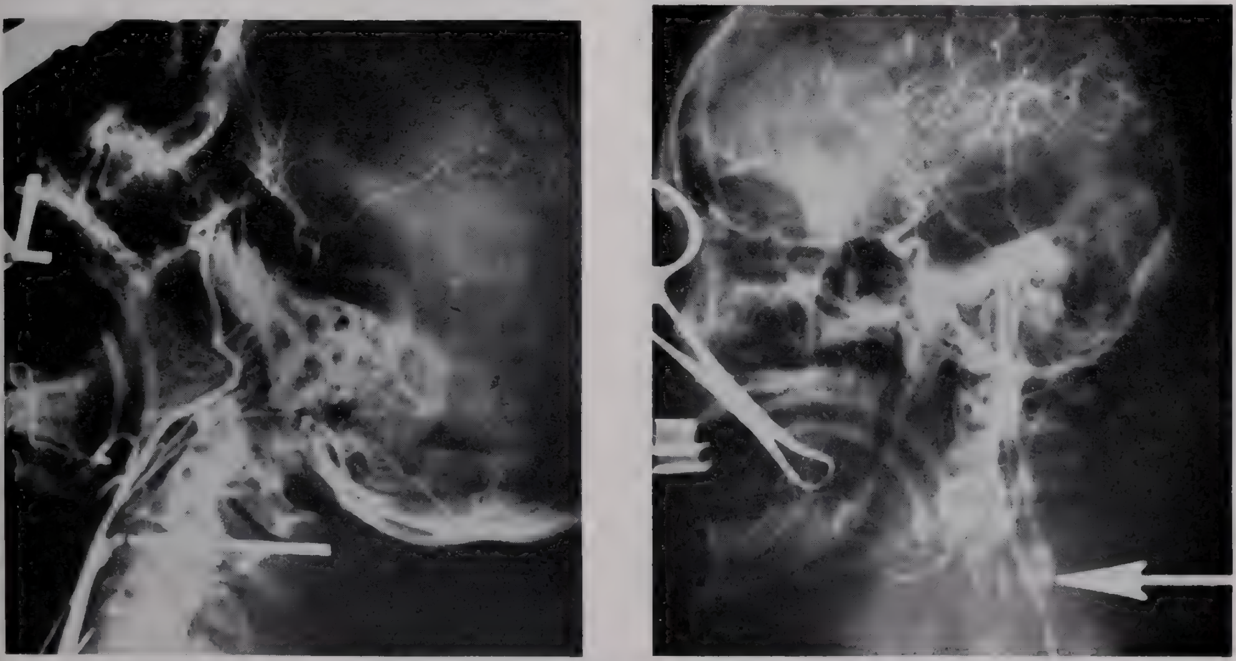

Fig. 3 — Duration of occlusion on the basis of history was nine days. (a-left) Preoperative arteriogram shows total occlusion of the carotid bifurcation. (b-right) Operative arteriogram following endarterectomy and thrombectomy shows restoration of flow and intracranial filling.

sion[12] restoration of flow in seven of 16 completely occluded internal carotid arteries, one three weeks after the onset of occlusion, led to the recommendation that endarterectomy be considered when on the basis of history the occlusion occurred within three to four weeks. His experience with the totally occluded internal carotid artery has been further extended, restoration of flow being accomplished in 13 of 24 cases operated, one case 22 days after the onset of total occlusion.[13]

Our experience parallels that of Gurdjian's, and it seems reasonable to explore the totally occluded carotid artery when by history the duration of occlusion is three to four weeks. In only one of the 12 successfully operated cases, Case 23, Table 2, was the duration of occlusion indeterminate. In six of 15 unsuccessful cases, Table 3, the duration of occlusion was indeterminate.

Restoration of flow in the totally occluded internal carotid artery did not cause worsening or death of the patient.

Wylie and Adams[24,25] reported six of 12 patients dying following restoration of flow in occluded arteries operated eight hours to two days after the onset of neurologic change and apparently stable at the time of surgery. They point to the hazard of perfusing ischemic brain tissue with blood at normal pressure. Four of their six deaths showed hemorrhagic infarcts at autopsy. Three of the 12 cases in which flow was restored in our series were operated in the acute phase of occlusion, eight, 11, and 36 hours after onset of symptoms. Two did well. One of these patients was operated in a state of coma 36 hours after his stroke and he never regained consciousness. Autopsy was not done.

Pertinent to this aspect of the problem, we have operated five patients with total occlusion of the common carotid artery. One patient was operated three days after the onset of a progressive stroke. Endarterectomy was unsuccessful and she died five days postoperatively. Autopsy showed massive, nonhemorrhagic, brain infarction. A second patient with chronic occlusion of the left common carotid artery had a subclavian to carotid artery anastomosis and died nine hours postoperatively. Autopsy showed massive, hemorrhagic infarction of the brain. A

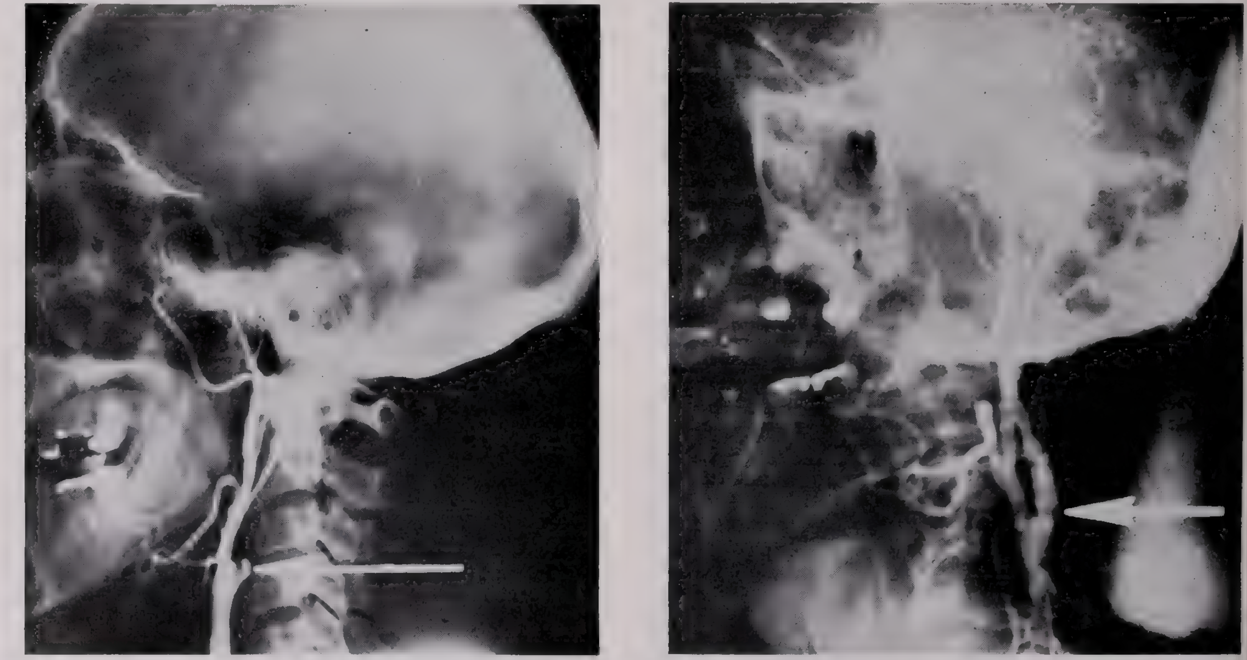

Fig. 4 — Duration of occluded internal carotid on the basis of history was 19 days. (a-left) Preoperative carotid arteriogram showing occlusion at the origin of the internal carotid artery and absence of intracranial circulation. (b-right) Following endarterectomy and thrombectomy, operative arteriogram shows restoration of flow and established intracranial circulation. An archogram seven days later for clarification of other extracranial vessels showed continued patency of the operated vessel.

third patient with progressive neurologic symptoms of one week's duration had total occlusion of the common carotid artery with a soft clot extending into the internal carotid artery. This was removed with a Fogarty balloon catheter and retrograde flow was established in the internal carotid artery. A graft was inserted on the ascending aorta and anastomosed to the common carotid artery proximal to the bifurcation, bypassing the chronic occlusion of the common carotid artery. Two days postoperatively he died. Autopsy showed marked subarachnoid hemorrhage and extensive encephalomalacia of the right cerebral hemisphere. Small areas of softening of the left occipital area and numerous petechial hemorrhages in the pons were also noted.

Two other patients with common carotid artery occlusion had subclavian to common carotid artery shunts, one with chronic occlusion of indeterminate duration and the other with occlusion of ten days' duration. This last patient also had significant stenosis of the opposite internal carotid artery, for which surgery was done. Both these patients did well. Although the factors producing hemorrhage in the brain following restoration of flow in occluded arteries are not entirely clear, the hazard must be recognized.

The consistent pathologic feature of these cases of totally occluded internal carotid artery has been chronic, atherosclerotic stenosis with a superimposed fresh thrombus that produces the total occlusion. With varying periods of time, the fresh thrombotic lesion propagates centrally. It seems reasonable, as with the management of other acute arterial occlusions, that anticoagulants be administered at the time that the diagnosis is established or suspected to prevent clot propagation.

Furthermore, our encouraging experiences with the use of Fogarty balloon catheters (three of four cases successful) in retrieving distal clot not otherwise removed by instrumentation and catheter suctioning, suggests that a more aggressive and persistent attack on these totally occluded arteries will lead to restoration of flow in a higher percentage of cases.

Summary and Conclusions

In a series of 140 patients with cerebrovascular insufficiency, in a six and one-half year period, 162 operations were carried out. Of special interest were 28 patients, 20% with total occlusion of the extracranial internal carotid artery.

Surgery was done on 27 of these patients, one of whom had bilateral occlusion of the internal carotid arteries. Thus, 28 totally occluded carotid arteries were explored. Restoration of flow by endarterectomy and thrombectomy was accomplished in 12 patients, 44.4%, or in 42.8% of the vessels operated.

The interval from the onset of total occlusion to the time that surgery was performed varied from 11 hours to 21 days. Contrary to most reports in the literature, restoration of flow in the totally occluded extracranial internal carotid artery is possible in a significant number of cases. The interval between the onset of total occlusion to the time of surgery need not be limited to a matter of hours and may, in fact, be weeks. On the basis of this experience, exploration of the totally occluded extracranial internal carotid artery is advised, if the duration of occlusion is within three to four weeks. Administration of heparin preoperatively, once the diagnosis is suspected or established, seems advisable, as in dealing with other acute arterial occlusions. The use of Fogarty balloon catheters as aids in performing thrombectomy merits further trial.

Addendum

Since presentation of this manuscript, four additonal patients have had successful restoration of the totally occluded extracranial internal carotid artery with the aid of Fogarty balloon catheters. Operative arteriograms have confirmed the restoration of flow.

References may be secured from the reprints.

The average man plays to the gallery of his own self-esteem. — Elbert Hubbard

Varnet's Syndrome*

(Jugular Foramen Syndrome)

This syndrome was first described by Varnet in 1918. It is evidenced by hoarseness, dysphagia of solids, and nasal regurgitation of fluids. The palate, pharynx, and larynx are involved, and the difficulty in swallowing is due to paralysis of the glossopharyngeal nerve which often causes a disturbance of taste over the posterior one third of the tongue.

The lesion occurs in the region of the jugular foramen where the ninth, tenth, and eleventh cranial nerves leave the skull at the hypoglossal foramen.

Paralysis of the vagus nerve results in dysphagia and hoarseness. Involvement of the spinal accessory nerve may cause paralysis and atrophy of the trapezius and the sternocleidomastoid muscle.

The lesion causing this syndrome may be a result of direct trauma, but can occur from an aortic aneurysm, carcinoma involving the esophagus, or from localized pressure from some other source.

Durham-Encyclopedia of Medical Syndromes
Paul B. Hoeber. Inc.

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*See Stapedectomy Page 1745.

Medical Men on Postage Stamps*

Albert Schweitzer (1875-1965), medical missionary to French West Africa, built at Lambarene, Gabon Province, a primitive hospital with his own and native labor, where, operating far into the night, he waged his relentless war against leprosy, sleeping sickness, and other tropical diseases. His heroic and noble work has been commemorated on postage stamps by Monaco in 1955, by Gabon in 1960, and by Germany in 1965.

Ephraim McDowell (1771-1830) was an American surgeon, who in 1809 performed the first operation recorded in the United States in ovarian surgery. In 1959 he was honored by the issuance of a U. S. postage stamp.

See Minnesota Med 49:1620, 1966.

In Brief

There are three stages in the history of every medical discovery. When first announced, people say that it is not true. Then, a little later, when the truth has been borne in on them, so that it can no longer be denied, they say it is not important. After that, if its inportance becomes sufficiently obvious, they say anyhow it is not new. — R. McNair Wilson

Derivatively Speaking

Fibula — from Latin *fig-bula* (a buckle)
Fistula — from Latin *fib-tula* (a pipe)

Coumarin-Induced Bleeding Complications

Report of Eight Unusual Cases from One Hospital

RICHARD L. REECE, M.D.
PHILIP A. OLSON, M.D.
Minneapolis, Minnesota

> *"Drugs can be standardized,*
> *but patients cannot."*
>
> *Herrman Blumgart, M.D.*
> *Professor of Medicine, Emeritus*
> *Harvard Medical School*

THE PHYSICIAN who prescribes anticoagulants trades the threat of thrombosis for the risk of hemorrhage. While the odds favor the physician, the patient suffers the consequences. In the last eighteen months at St. Barnabas Hospital, a 315-bed institution, eight patients have presented with unusual coumarin-induced complications. Because awareness of similar complications may lead to proper treatment in future patients, we believe their histories are worth telling.

Case Report

*Epidural Hematoma**

A 51-year-old engineer was admitted on September 12, 1964, with a four-day history of chest pain radiating to the back and shoulders. He had had two previous myocardial infarctions and had been receiving bisoxycoumarin (Dicumarol) since 1962. Physical examination was normal. His laboratory work included a hemoglobin of 14.7 gm.%, a white blood cell count of 12,000 with 80 neutrophils, 40-50 red cells/h.p.f. in the urine, and a prothrombin time of 39 seconds (control 12.2 seconds).

On the second hospital day he developed tender neck muscles with ecchymoses of the skin. The prothrombin time was then 36 seconds. On the fourth day he became quadriplegic. A lumbar puncture showed 15,000 rbc. and a protein of 4.7/100 ml. A myelogram demonstrated a complete block (Figure 1). A cervical laminectomy was performed, but he died shortly after the operation.

At autopsy, a large organized epidural hemorrhage compressed the anterior spinal cord. Other organs were free of hemorrhage. The cause of death was a perforated gastric ulcer with diffuse peritonitis.

Comment

Central nervous system hemorrhage is a dreaded complication of coumarin therapy and calls for evacuation of the offending hematoma. Patients on anticoagulants may bleed into the epidural or subdural space or intracranially.[2-4] Bleeding can occur while the prothrombin time is at supposedly safe

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*This case report has previously appeared as the subject of a Clinical Path Conference in *Minnesota Med* 49:145, 1966.

levels. Eight of the ten patients with coumarin-induced epidural hemorrhage reviewed by Spurney *et al.* had prothrombin times within the therapeutic range.[2] A diagnostic clue in patients with cord compression from epidural hemorrhage is xanthochromic cerebrospinal fluid with a decreased pressure and an increase in protein control (Froin's syndrome). Laminectomy and decompression after coumarin withdrawal and vitamin K infusion are the most effective means of therapy.

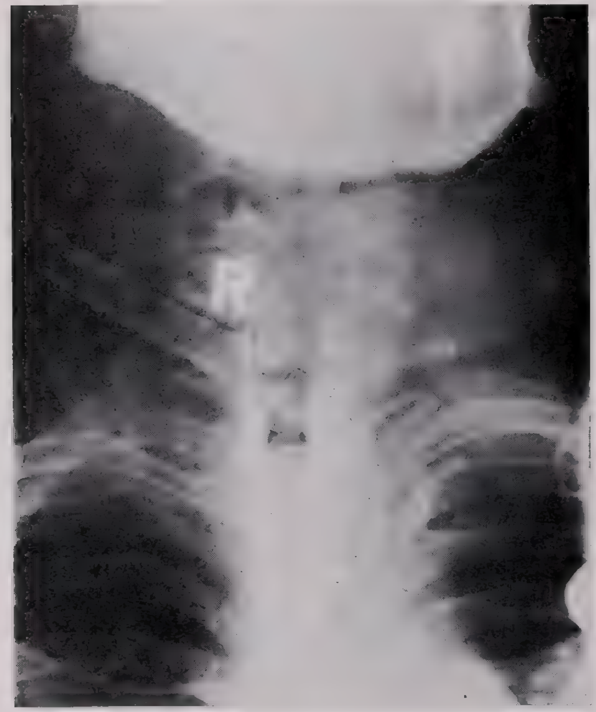

Fig. 1 — Myelogram showing complete obstruction of pantopaque at the level of the disc space between the 6th and 7th cervical vertebrae. The spinal cord is widened by external pressure. The lateral film showed anterior extradural compression.

Probable Hemoperitoneum

A 47-year-old woman was seen on August 12, 1965, with a one-week history of vague cramping abdominal pain and constipation. One day before admission she had experienced nausea and vomiting. She had been taking bisoxycoumarin for five weeks because of thrombophlebitis. On physical examination, her abdomen was soft, distended and silent. She complained of right upper quadrant tenderness, and the provisional diagnosis was subacute cholecystitis.

The hemoglobin was 13.8 gm.%, the white blood cell count 10,600 with 75 neutrophils, and the prothrombin time 71 seconds (control 13.5 seconds). Both the urine and vomitus registered a positive benzidine test for occult blood, and 25 rbc./h.p.f. were seen on urinalysis. The abdominal flat plate showed a non-specific ileus. Because of the possibility of a hemoperitoneum from anticoagulants, vitamin K_1 (Aquamephyton) was given. Within hours the prothrombin time dropped to 21 seconds. By the next day her pain had subsided, and she was expelling flatus. She was discharged four days after admission.

Comment

This patient's symptoms and course are in keeping with coumarin-induced peritoneal bleeding. The clinical picture of hemoperitoneum simulates intestinal obstruction because of cramping, obstipation, and vomiting.[5] The bowel sounds are depressed or absent, and tenderness may occur in any quadrant. The diagnosis is best established by needle aspiration of the peritoneum. The

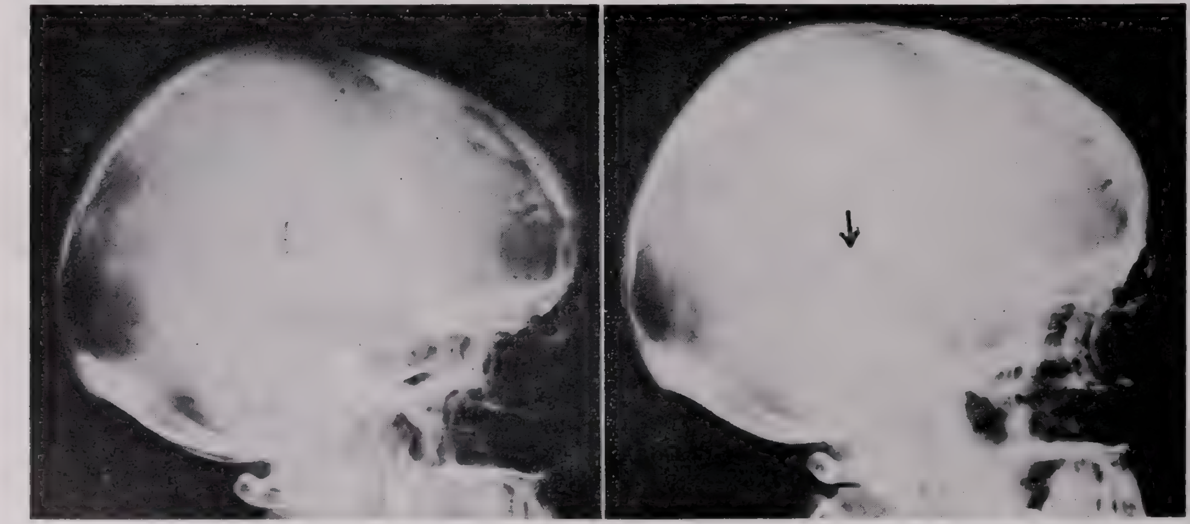

Fig. 2 — Lateral skull films demonstrating one cm. depression of pineal gland. The film on the left was taken on October 5 and the film on the right was done on November 30. The downward shift of the pineal led to evacuation of subdural hematomas.

free blood remaining may produce fever but usually leads to no other complications.

Probable Retroperitoneal Hemorrhage

A 36-year-old female entered the hospital on October 30, 1965, with a complaint of abdominal pain and back pain. One week before admission she had had a three-day illness with a fever of 105 and generalized muscle aches. Her symptoms were not improved by aspirin, and she saw a physician. He made a diagnosis of an acute viral illness, and she was given prophylactic dimethylchlortetracycline (Declomycin). Two days before her hospitalization, she had severe right lower quadrant pain radiating to the right costovertebral angle. The pain required morphine for relief and was thought to be due to a renal stone.

The patient had been hospitalized three weeks previously for coronary insufficiency and was placed on warfarin sodium (Coumadin) 5 mg. daily. She had been hypertensive for three years, but her blood pressure was easily controlled at 120-140/80-90 with hydrochlorothiazide and reserpine.

On physical examination she was in acute distress from severe abdominal pain. Her blood pressure was 140/90, and her temperature was 99.2. She displayed deep lower abdominal tenderness with mild rebound tenderness. An occasional bowel sound was heard. On pelvic examination tenderness was elicited high in the cul-de-sac.

Laboratory data included a hemoglobin of 12.0 gm.%, a white blood cell count of 10,000, a sedimentation rate of 92 mm/hr., a urine specific gravity of 1.015 with 4 rbc./h.p.f., BUN. of 17 mg./100 ml. and a prothrombin time of "greater than" 60 seconds (control 13.5 seconds).

The patient failed to pass urine for the first 24 hours. An emergency intravenous pyelogram was done, and no contrast material was seen in the calyces or bladder after four hours. A cystoscopy was performed, and indwelling ureteral catheters were inserted with immediate flow of urine. The urine obtained at cystoscopy was bloody. At this point, the patient's hemoglobin had fallen sharply to 9.8 gm.%, and she was given one unit of packed cells. The provisional diagnosis was retroperitoneal hematoma with ureteral obstruction and probable blood clots in the calyces. She was given 50 mg. of vitamin K_1 (Aquamephyton) on October 31 with a prompt decline in the prothrombin time to 16 seconds. For a week after the insertion of the catheter, urine drained mostly from the right kidney; the unequal drainage was attributed to clots in the left kidney. The drainage then equalized. The catheters were removed, and she was discharged on November 12.

Comment

Before her febrile viral illness, this patient's prothrombin time was well controlled. Did her illness or its treatment with aspirin and declomycin produce hypoprothrombinemia? Fever, salicylates, and broad-spectrum antibiotics are all known factors in producing a prolonged response to coumarin.[6,7] Although the mechanism of the effect of fever and aspirin on the prothrombin time is not clear, antibiotics act by interfering with the synthesis of vitamin K in the intestine.

The site of the patient's blood loss is guesswork. The fall in the hemoglobin from 12.2 gm.% to 9.8 gm.% indicates significant hemorrhage, and the retroperitoneal space seems a logical reservoir for a large amount of blood. Her complaints of costovertebral pain, the tenderness high in the cul-de-sac, and the prompt excretion of urine after the placement of a ureteral catheter add to the evidence from a retroperitoneal hematoma with ureteral obstruction. Retroperitoneal hemorrhage does not explain the roentgenographic picture of renal failure. The bloody urine obtained at cystoscopy could reflect parenchymal or calyceal hemorrhage.

Bilateral Subdural Hematoma

A 59-year-old widow was admitted on November 11, 1965, for evaluation of generalized severe headache. She had been hospitalized two months previously for vertigo. This was attributed to cerebro-

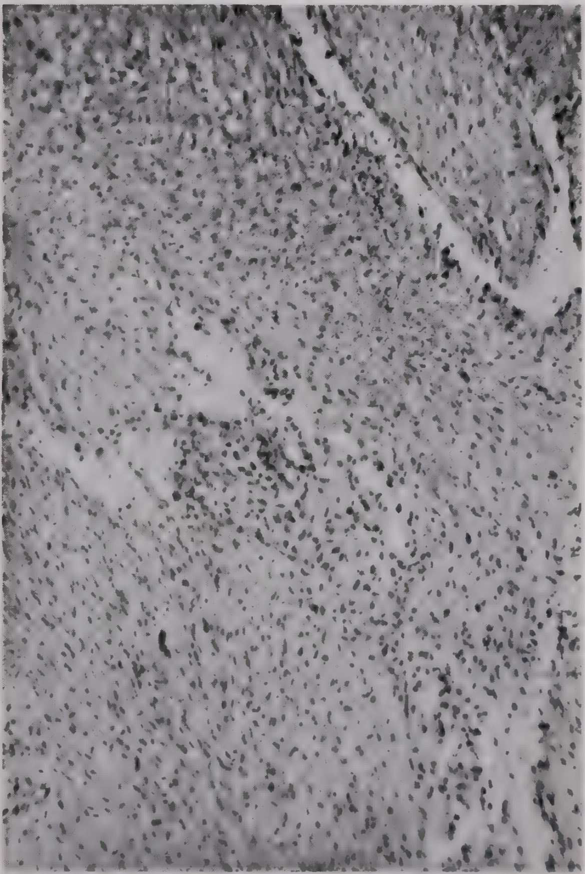

Fig. 3 — Low-power view of subdural hematoma showing fibroblastic proliferation. The histological appearance suggests a chronic subdural hematoma of at least three weeks' duration.

vascular arteriosclerosis. She was placed on bisoxycoumarin, 50 mg. daily. Her headaches began two weeks before admission and became steadily worse.

A neurological examination was negative, but the patient complained of persistent headache. Laboratory work included a prothrombin time of 21 seconds (control 14.2 seconds). The patient's headache was considered "functional," and she was treated with trancylcypromine (Parnate), trifluoperazine (Stelazine), and chloral hydrate.

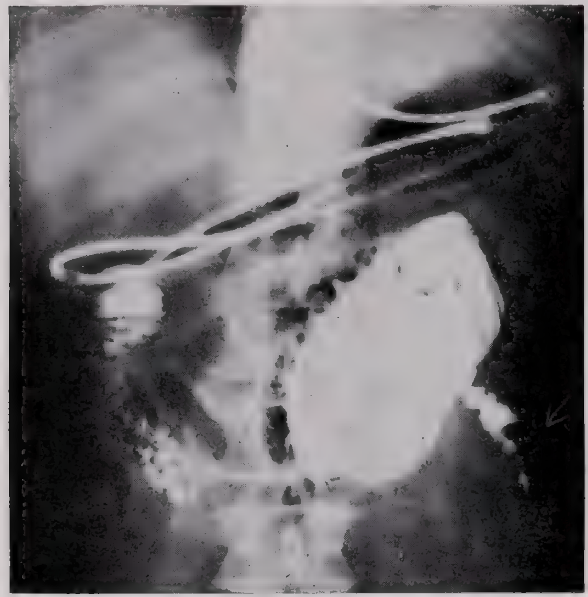

Fig. 4 — Small bowel contrast study on January 16, showing complete obstruction of proximal jejunum. The bowel wall around the obstruction is thickened and forms a soft tissue mass due to an intramural hematoma.

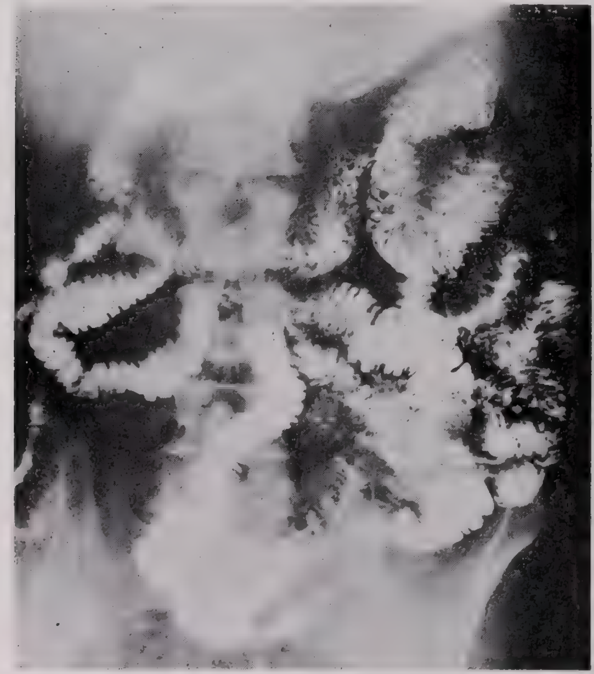

Fig. 5 — A repeat small bowel study on January 24, demonstrating resolution of small bowel obstruction with residual thickening of bowel wall and feathery mucosal pattern of the jejunum.

A lumbar puncture of November 23 yielded xanthochromic fluid containing 515 rbc./mm^3 and a protein of 104 mg./100 ml. A brain scan and carotid arteriograms were normal, but a skull film on November 30 showed definite depression of the pineal when compared to the previous examination of October 5. (Figure 2). On December 1, a bilateral craniotomy was performed with the removal of bilateral "subacute" subdural hematomas. Microscopically, the hematomas showed organization with fibroblastic reaction and fibrous tissue formation (Figure 3).

Comment

This patient illustrates a treacherous feature of therapy with coumarin compounds; viz., patients may bleed at ostensibly safe prothrombin levels. In a previous article, one of us (RLR) reviewed 15 patients with "spontaneous" subdural hematomas — seven with prothrombin times in the therapeutic range.[8] About 75% of patients with subdural hematomas usually have a history of trauma, but in anticoagulated patients subdural hematomas tend to be spontaneous or initiated by a minor event such as straining during a bowel movement.[8,9]

Intramural Hematoma of the Jejunum

A 55-year-old pharmacist entered the hospital on January 15, 1966, complaining of abdominal pain of four days duration. He had had a myocardial infarction in 1959 and had been placed on warfarin sodium (Coumadin). Between 1959 and 1960, he had had two episodes of skin purpura and was erratic in taking the drug and in having prothrombin determinations. For four days prior to his January 15th admission, he had experienced increasingly severe abdominal pain culminating in repeated vomiting.

On examination, he was pale and in distress from abdominal pain. The blood pressure was 120/80 and the pulse 110. The abdomen was distended with left lower quadrant tenderness and rebound tenderness. A mass was palpable in the tender area. The bowel sounds were high-pitched. Petechia was present over the legs.

The hemoglobin was 14.2 gm.% and the white blood cell count 15,100 with 65 neutrophils and 19 band forms. The urine contained 30-50 rbc./h.p.f., and the prothrombin time was 59 seconds (control 14.0 seconds). He was given intravenous vitamin K_1, and the prothrombin time dropped to 20 seconds within six hours.

An abdominal flat plate disclosed loops of small bowel with air fluid levels and a soft tissue density. An upper gastrointestinal series showed a soft tissue mass and an obstructed jejunum (Figure 4).

The patient was treated with nasogastric and then Miller-Abbott suction. He promptly improved, with resolution of the obstruction (Figure 5), but on January 24, his speech became slurred and his left side became paralyzed. He improved with heparin anticoagulation, but on January 29 went on to a complete left hemiplegia.

Comment

This patient's clinical symptoms and signs and radiographic picture are characteristic for intramural hematoma of the jejunum. Goldfarb, in reporting eleven similar cases and reviewing 24 from the literature, observed that: patients usually have a distended abdomen and high-pitched bowel sounds; the site of obstruction is almost always the jejunum; the obstruction is reversed in two to three days by withdrawal of anticoagulants, vitamin K infusion, and intestinal intubation.[10] The most characteristic radiographic sign, as seen in this patient and other reported cases, consists of a narrowed rigid segment of bowel with a serrated mucosal pattern, which is called the "crescent" or "thick bowel" sign.[11]

The cause of this patient's hypoprothrombinemia could have been excessive self-administration of warfarin sodium. He was a pharmacist, and seven of the ten "Dicumarol-Eaters" reported by Bowie et al. were connected with the medical profession in some way and had free access to anticoagulants.[12] Patients who consume anticoagulants without prothrombin time control are destined for hemorrhage. Lastly, this patient's stroke nine days after cessation of warfarin raises the spectre of "rebound hypercoagulatability" — a phenomenon which occurs seven days after stopping the drug.[13]

Paralytic Ileus — Bleeding Site Unknown

A 74-year-old retired white male entered the hospital on February 5, 1966, complaining of severe abdominal pain. His pain had started abruptly three days before when he had grabbed a stair rail after stumbling on the stairs. He had obstipation but no vomiting. He had been taking warfarin sodium for one month after an episode of cerebral ischemia.

On examination, his pulse, blood pressure, and temperature were normal. He had diffuse abdominal tenderness with slight distention and generalized rebound tenderness. The abdomen was silent. A 2-cm. ecchymotic area was noted on the abdominal wall.

Laboratory data included a hemoglobin of 12.6 gm.%, a wbc. of 12,300, a prothrombin time of 107 seconds (control 12.5 seconds), and 100-150 rbc./h.p.f. in the urine. A plain film of the abdomen showed large and small bowel distention and was interpreted as a paralytic ileus. A contrast study showed no obstruction of the intestine.

The patient was given 50 mg. of intravenous vitamin K_1, and a nasogastric tube was inserted. Within eight hours his prothrombin time had dropped to 18 seconds, and his abdominal pain was subsiding. By the following morning he was passing flatus. Two days after admission, he had a transient hematuria but no recurrence of abdominal symptoms. He was discharged nine days after admission.

Comment

Either bleeding into the mesentery or the peritoneal cavity could have produced paralytic ileus in this patient. The absence of changes in the jejunum and the lack of obstruction make an intramural hematoma unlikely. The response to vitamin K and intestinal intubation is a succinct testimonial to a statement by Hafner concerning coumarin-induced intestinal ileus: "This is a non-surgical problem — an awareness of its existence is imperative in order to obviate needless operative intervention."[14]

Hemorrhage into Metastatic Cerebellar Mass

A 67-year-old female was admitted on March 28, 1966, because of dizziness for two weeks and vomiting for one week. The dizziness occurred with a change in position of the head and was particularly noticeable when she stood after lying down. She observed she tended to veer to the right while walking.

On physical examination she was an alert asthenic

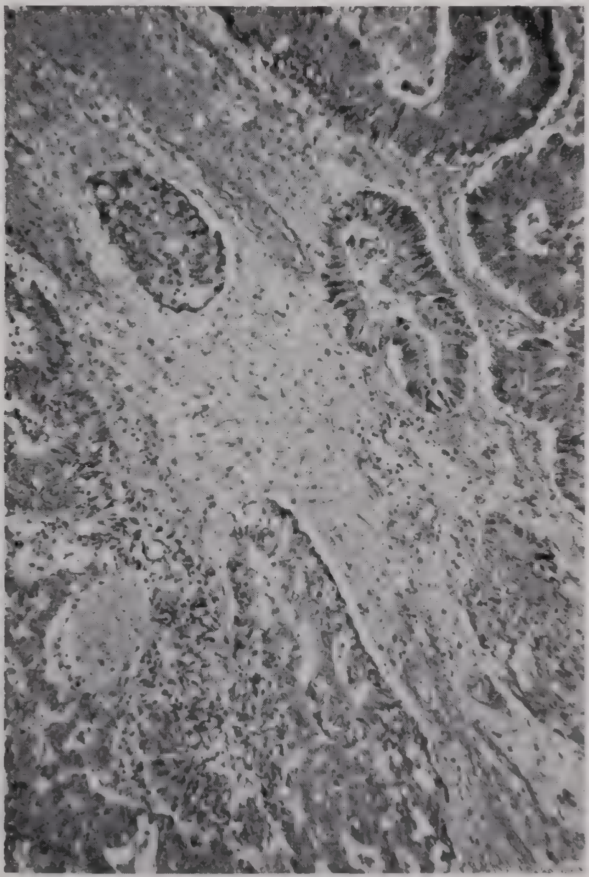

Fig. 6 — Section of cerebellar hematoma showing clumps of metastatic adenocarcinoma. H&E 100 ×

female. Her blood pressure was 162/90. A bruit was heard over the right carotid and subclavian arteries. The admitting diagnosis was arteriosclerosis of the right subclavian artery with resultant vertebral basilar artery insufficiency.

A spinal tap was done, and the fluid was clear with a normal protein content. On the second hospital day, she vomited repeatedly after a glucose tolerance test. On April 1, 1966, a retrograde brachial arteriogram showed sclerosis of the right innominate artery. On April 2, 1966, she was given 40 mg. of warfarin sodium and on April 3 she received 20 mg. of the drug. Her prothrombin times from April 2 to April 5 were 13, 17, 33, and 47 seconds. On April 5 she became lethargic and then lapsed into coma with cyanosis. She died on April 5.

At autopsy, a 4 by 4-cm. hemorrhagic mass occupied the cerebellum, and 50 ml. of blood were in the subarachnoid space. Microscopically, the cerebellum revealed metastatic adenocarcinoma cells floating in pools of red cells (Figure 6). The primary tumor was an annular, ulcerating carcinoma of the sigmoid colon.

Comment

This patient was given warfarin for presumed cerebrovascular insufficiency and four days later hemorrhaged into a cerebellar metastasis. Brain hemorrhage is the most frequent cause of death from anticoagulants; it accounted for 46 to 122 deaths in Russek's series[15] Despite the threat of fatal hemorrhage, coumarin therapy is established in patients with vertebral-basilar insufficiency. In a Mayo Clinic study, ischemic attacks stopped in 90 of 94 patients after starting anticoagulant therapy.[16] In the same study, 107 patients with vertebral basilar thrombosis had a mortality of 8 percent on coumarin as compared to 58 percent in 31 similar patients.

Ruptured Abdominal Aneurysm

A 78-year-old white male was admitted to St. Barnabas Hospital on April 9, 1966, with hematuria of four days duration and nasal bleeding of one day duration. He had been taking "various" drugs at home, including thorazine and acetosalicylic acid.

The patient had been in St. Barnabas in December of 1965 for cerebral vascular insufficiency. At that time there was loss of coordination of the left arm and leg. He also complained of shortness of breath after physical exertion. Neurological examination revealed no special weakness in either arm, and the reflexes were completely normal. After two days of bisoxycoumarin therapy, the patient was discharged with a prothrombin time of 29 seconds.

When admitted on April 9, the prothrombin time was 108 seconds, and intravenous vitamin K_1 was quickly given. By the morning of April 10, 1966, the prothrombin time was still 81, but nasal bleeding and hematuria had stopped and the patient was feeling better and alert. The hemoglobin was 12.5 gm.%. His urine contained numerous red cells. Ab-

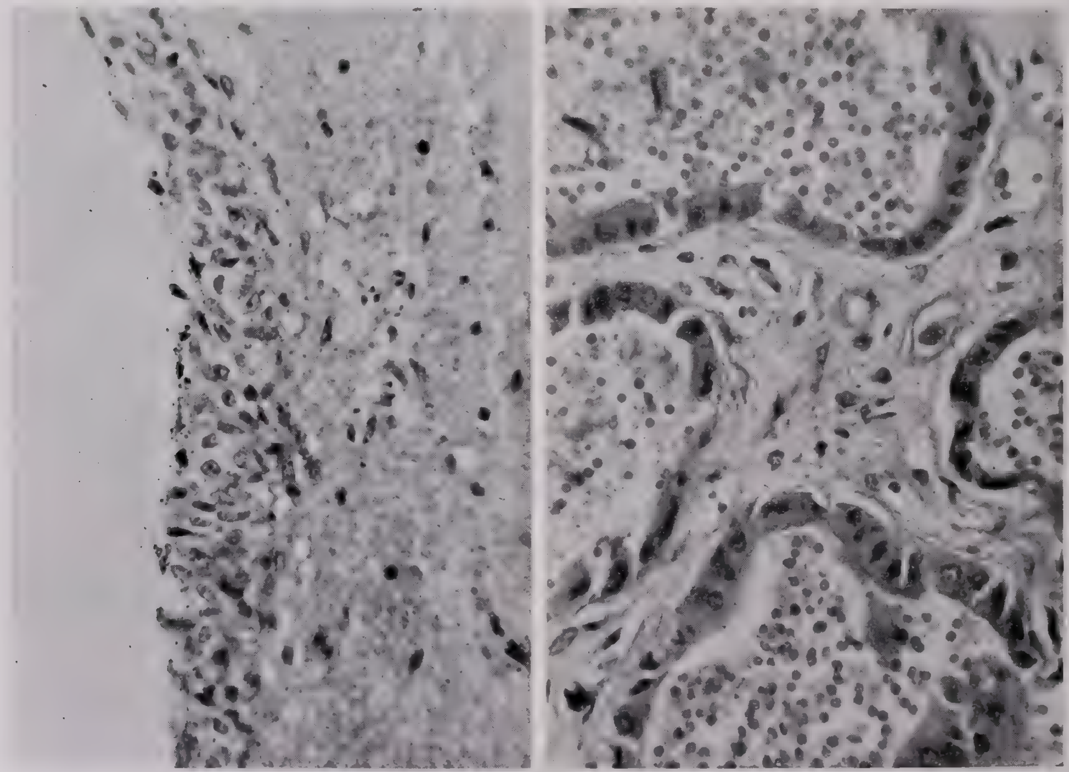

Fig. 7 — Photomicrographs showing blood in renal tubules and blood dissecting beneath the epithelium of the renal pelvis. H & E 430 ×. The patient had hematuria; and the left renal pelvis and bladder were filled with blood at autopsy.

dominal examination was considered negative, and the neurological examination was normal. By April 11, 1966, the prothrombin time was 22 seconds, and bisoxycoumarin was again given. On the morning of April 12 the patient had bloody urine again and passed two bloody stools. He complained of severe abdominal cramps and pain. Despite the administration of demerol, the abdominal pain became more severe. The abdomen was distended. At about 8 o'clock on the morning of April 12, the patient collapsed while in the bathroom and had convulsions. He was helped back to bed and after a short time responded to verbal stimuli. The blood pressure at 8:20 a.m. was 120/100, and the skin was cool and clammy. Aramine was given when the blood pressure became unobtainable. Examination showed hyporeflexia with positive toe signs, bilateral Babinski, a distended and silent abdomen. One examiner described the pupils as fixed and equal and the right arm as weak and flaccid with a definitely positive Babinski also on the right. The patient died at 8:30 p.m.

At autopsy the peritoneal cavity and root of the mesentery contained over 1000 ml. of blood. The source of the blood was a ruptured abdominal aneurysm. Other sites of bleeding were the wall of the sigmoid colon, the lung, and the renal parenchyma (Figure 7). The left kidney pelvis was filled with blood as was the bladder. The brain showed no lesions except for sclerosis of the cerebral vessels.

Comment

Anticoagulants were not directly responsible for this patient's death, but they contributed to it by clouding the true diagnosis and exaggerating the bleeding from the aneurysm. Bleeding itself can prolong the prothrombin time and should be searched for in the absence of a clear-cut cause of hypoprothrombinemia.[17] Patient reliability should be a prime consideration in prescribing coumarin drugs. The possibility exists that this elderly man, confused by his cerebrovascular disease or his sedatives, took an inadvertent overdose of coumadin.

Discussion

The word "dilemma" is rooted in the literature on anticoagulation. These dilemmas may be: complications are merely an extension of the therapeutic effect; bleeding can occur in the "therapeutic range"; the index of anticoagulant response — the prothrombin time — is often poorly controlled and, indeed, is expressed differently by different laboratories; anticoagulants are influenced by underlying diseases and by other drugs; and the indications for anticoagulants are controversial.

To these dilemmas could be added a clinical maxim: "Expect the unexpected." Patients on anticoagulants can and do bleed in any location: subdural space, brain, pituitary, pericardium, pancreas, adrenal, kidneys, retroperitoneal space, wall of the intestine, and rectus abdominis muscle; and they may present with such rare syndromes of medical progress as generalized clotting deficiencies, "purple toes" necrosis of the skin, and gangrene of the breast.[2,4,10,12,15,19-25] Recognition of these complications by the doctor can be life-saving for the patient.

What is the risk of anticoagulation? The answer differs with the observer. The authors of the authoritative textbook, *Pharmacological Basis of Therapeutics*, state that the taker of bisoxycoumarin has a 4% incidence of minor bleeding and a 2% chance of major hemorrhage.[6] Yet Keyes and his followers observed bleeding in 42% of their patients, and 13% were classified as major.[26] Tullock and Wright reported a 19% incidence of bleeding, but 11 of their 71 patients with bleeding required vitamin K or transfusions.[27]

Results from well-controlled studies of coumarin therapy probably did not reflect the experience of practicing physicians. In 1953, Russeck and Zohman sent a questionnaire to internists and cardiologists, and of 228 physicians replying, 104 had seen patients with serious complications and 122 deaths attributed to hemorrhage.[15]

The purpose of this report is not to discuss the tangled controversy of indications and statistical dangers but to highlight unexpected complications and why they occur. Giving coumarin drugs is not a simple matter of administering the drug and following the prothrombin time. The results of "prothrombin" tests differ, not only among various laboratories, but in the same laboratory.[28] This may be due to differences in diluents, in dilution curves, in the types of thromboplastin used, to modified technique, to technician errors, or to the times and differences of temperature used in incubating the plasma.[28]

Yet another controversy simmers as to whether the Quick prothrombin time measures the deficiency of factors responsible for bleeding.[29] Quick himself has countered these claims by asserting that the standard prothrombin time, properly performed, is adequate for control of coumarin therapy.[30] The papers referred to contain excellent discussions of the effect of coumarin drugs on the clotting mechanism and on the various coagulation factors.

The dilemma of the clinician is compounded by conditions and drugs which obscure and complicate anticoagulation. Fever, blood dyscrasias, hepatic dysfunction, renal insufficiency, hypertension and ulcerative gastrointestinal disease all increase the risk of bleeding. Indeed, hemorrhage is often the first sign of the existence of underlying disease.[31] Among drugs which alter the response of patients are steroids, salicylates, barbiturates, broad-spectrum antibiotics, and prophyl thiouricil.[32] Ulcerogenic drugs, such as cincophen, phenylbutazone, and reserpine, do not effect the prothrombin time but should be avoided to decrease the threat of gastrointestinal bleeding. The physician who prescribes anticoagulant should be aware of the effect of drugs and disease before deciding whether the expected benefits outweigh the potential dangers.

Summary

Eight patients were admitted to St. Barnabas Hospital from September, 1964, to April, 1966, with serious complications from coumarin therapy. The known site of hemorrhage in five patients was the spinal epidural space, the wall of the small intestine, the subdural space, the cerebellum, and an abdominal aneurysm, and in three, the suspected sites of bleeding were the retroperitoneal space, the root of the mesentery, and the peritoneal cavity. Three patients died; one was saved by exacuating a bilateral subdural hematoma; and four recovered after cessation of coumarin therapy and vitamin K administration.

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15-32 May be secured from the author or the reprints.

Disordered Metabolism

Now, is it not a disgraceful state of affairs that a person who has had an excellent constitution should need to be carried about by other people owing to gout, or should be worn away by the pains of stone or colic, or of a bladder ulcerated by disordered humours (cacochymy). Is it not disgraceful that a person should, by reason of that extraordinary thing, arthritis, be unable to use his own hands, and should need somebody else to bring food to his mouth, and to perform his toilet necessities for him? Unless one were an absolute weakling, one would prefer to die a thousand deaths rather than endure such a life. — Galen

Augmentation Mammaplasty

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SINCE THE subject of augmentation mammaplasty often gives rise to adverse criticism, one might wonder whether or not there ever is any acceptable excuse for performing this type of cosmetic surgery. Justification for such surgery seems dependent entirely on the patient's motives for wanting such alterations in breast contour. It is well to bear in mind that the underlying factors prompting a woman to seek the services of a surgeon for correction of a flat chest or underdeveloped breasts may appear unreasonable to many people but are perfectly rational to the patient herself. Although the motives often are obscure many women, when comparing their small breasts with those of their friends more generously endowed, feel sensitive and self-conscious. Many stable and well-integrated women can be embarrassed over a flat chest, and it is gratifying to observe the satisfaction which these individuals experience and the favorable personality changes which they often exhibit after a successful mammaplasty (Figures 1, 2, and 3). It therefore becomes evident that an augmentation mammaplasty is of much psychologic benefit in some cases of mammary hypoplasia.

It is true that the availability of padded bras and so-called "falsies" solves the problem for many women with hypoplastic breasts, but in some cases the use of such devices does not remove the emotional distaste for this imperfection in body contour. In these instances, nothing short of an augmentation mammaplasty will help the patient obtain inner security and self-esteem.

Unfortunately, in a great many cases, the desire for surgical enlargement of the breasts is prompted by motives far removed from physical attractiveness. I am referring to patients who foster the unrealistic hope that alterations in breast contour will solve everything from a nonexistent love life to the most involved marital difficulties; needless to say, nothing is farther from the truth.

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Women who request augmentation mammaplasty can be divided into two categories: those who will benefit psychologically by this form of surgery and those who will not.

Indications

I have no hesitancy in recommending a cosmetic mammaplasty on women with hypoplastic breasts whose desire for surgery is prompted merely by an inclination to improve their physical appearance. Delving into the psychologic past of such an individual often reveals the fact that she has had a lifelong feeling of self-consciousness; her request for breast surgery involves nothing more than a desire for improvement in body contour, hoping thereby to eliminate her feelings of inferiority. In all such cases, an augmentation mammaplasty is especially helpful in giving the patient a sense of emotional well-being.

Such patients are not to be confused with the woman who has a deep-seated, almost pathologic sense of inferiority, which makes it impossible for her to cope with the emotional problems of everyday life, and who attributes such feelings of inadequacy entirely to small or unattractive breasts. Such a person often is of the opinion that an augmentation mammaplasty will give her an immediate sense of self-confidence. However, such is not the case, and the patient finds that after surgery her emotional pattern continues along the same old lines with no relief from inner conflicts and no increase in self-esteem.

Contraindications

Any woman with mental or emotional problems not related to the breasts but which the patient ascribes directly or indirectly to underdeveloped mammae should be discouraged from undergoing an augmentation mammaplasty; as a matter of fact, the surgeon should flatly refuse to operate on such a person.

Shattered Romance

In this category are women who, for various reasons, do not attract members of the opposite sex; however, if the breasts are surgically enlarged because of such circumstances, the patient is in for bitter disappointment when she finds that it has not

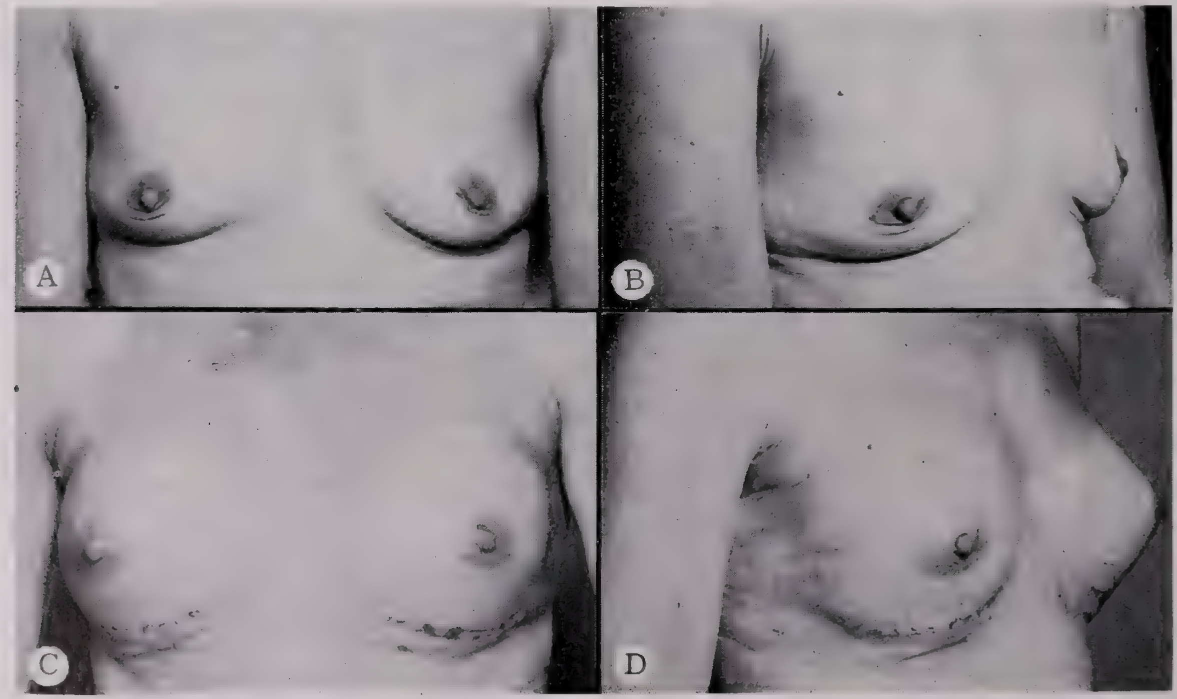

Fig. 1. Hypoplastic breasts. *A* and *B*, Before insertion of implants. *C* and *D*, After.

opened the way to romance. Then there are married women who believe that an augmentation mammaplasty will dissolve a whole host of marital difficulties, the most common of which are disinterest or unfaithfulness on the part of the husband. Needless to say, these operations not only do not relieve these unpleasant situations but actually compound the patient's problems. Apparently the causes of such difficulties are incomprehensible to the patient but become buried in a mass of inner conflicts and emotional upheavals. To such a person, the enlargement of the breasts seems to be the only means, or at least one means, of relieving her depressing and often insurmountable problems. She

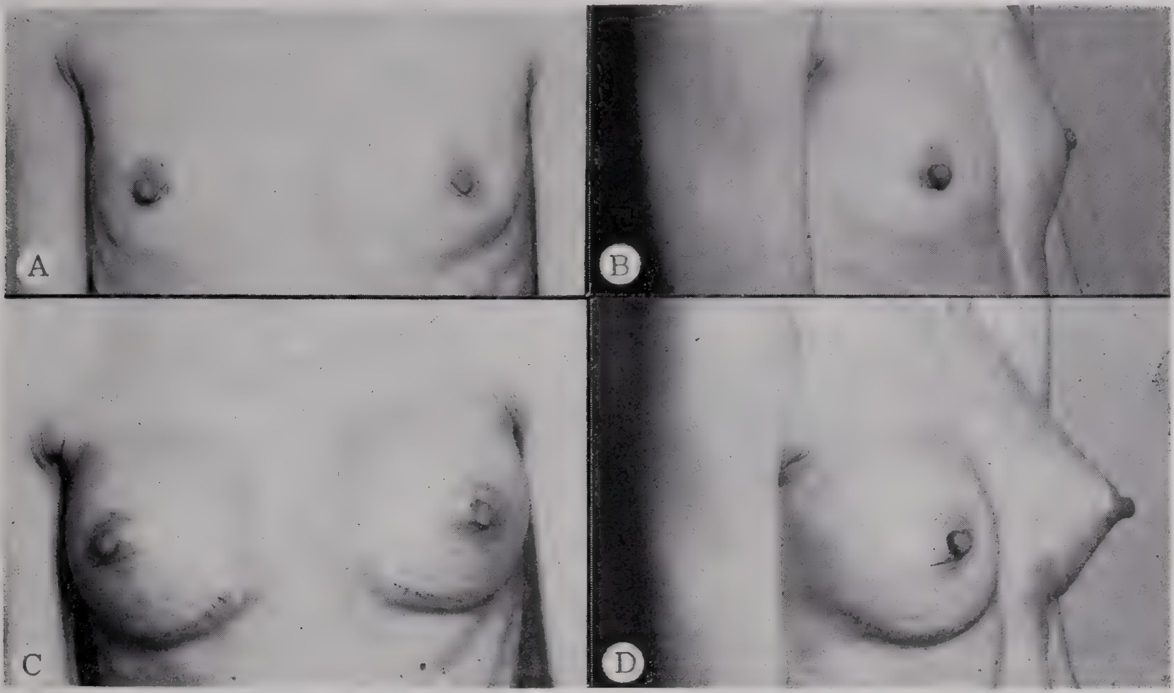

Fig. 2. Hypoplastic breasts. *A* and *B*, Before insertion of implants. *C* and *D*, After.

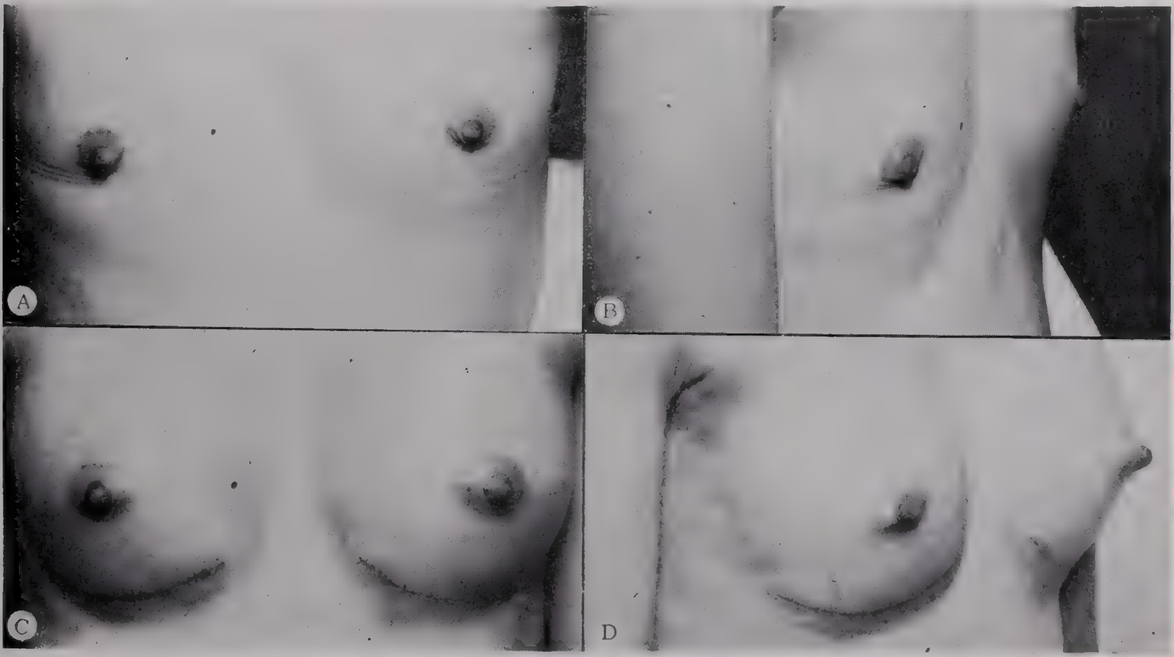

Fig. 3. Hypoplastic breasts. *A* and *B*, Before insertion of implants. *C* and *D*, After.

feels that enlargement of the breasts will improve her figure to the point where an unfaithful husband or an indifferent lover will take renewed interest in her, thereby avoiding the possibility of divorce or a broken love affair. Shattered romances and disillusionment in marriage, however, are among life's difficulties not solved by altering the contour of the breasts.

Pleasant Surprise

Many wives want this type of surgery performed without their husbands' knowledge and consent. Not infrequently, a wife wishes to undergo the surgical procedure when her mate is out of town, thereby hoping to surprise him when he returns. However, it usually is the wife who is surprised, because I have yet to encounter a disinterested or unfaithful husband who is overjoyed to find, when he returns home, that his wife has spent several hundred dollars having her breasts enlarged. Operating on such women leads to so many problems that most plastic surgeons refuse to perform an augmentation mammaplasty on any married woman without her husband's consent.

Psychopathic Personality

Finally, I would like to mention the fact that psychopathic individuals not infrequently seek alterations in breast contour for reasons not always apparent. Surgical enlargement of the mammary prominences solve nothing in such cases and can lead the surgeon into unpleasant situations. Even more distressing are the difficulties encountered when the unsuspecting surgeon performs a mammaplasty on a psychotic woman who seems normal before the operation but postoperatively reveals unmistakable evidence of her distorted mind.

From the foregoing discussion, it should be apparent that the psychologic aspects of patients wanting an augmentation mammaplasty are deep and complicated. If the surgeon is going to avoid difficulties in these cases, it is most important for him to realize that every woman who consults him in regard to an augmentation mammaplasty is not a fit candidate for this type of cosmetic surgery. He must explain in detail to the patient, and to her husband as well, the problems involved and the possible complications. In addition, he must not promise precise postoperative results which cannot always be surgically achieved. Furthermore, if the surgeon is unable to evaluate the patient's emotional background, he had better seek the services of a competent psychiatrist before performing the operation. Patients thus properly selected and warned against expecting too much or the impossible are going to be pleased with the final result and not disgruntled should a complication arise.

Methods

In general, there are three methods of enlarging the breasts at the present time: (1) transplantation of free dermal-fat grafts; (2) transference of submammary dermal-fat pedicle grafts; and (3) submammary insertion of plastic sponges or other plastic materials.

Free Dermal-fat Graft

When free dermal-fat grafts, usually obtained from the buttocks are employed to increase the size of the breasts, the results usually are unsatisfactory. Much of the fat in such transplants undergoes gradual liquification and absorption. In fact, practically all of the graft eventually disappears.

Dermal-fat Pedicle

Theoretically, inframammary dermal-fat pedicle flaps supply tissue which will not shrink or disintegrate because the graft has its own blood supply through the pedicle. Unfortunately, this method of augmenting the size of the breasts has some unfavorable features which make the procedure undesirable in most cases. Not only does it occasionally lead to some conspicuous scarring in the submammary region but inadequate mammary enlargement or poor contour occurs in many instances because an insufficient amount of tissue is available for transplantation. Most women who have a flat chest or insignificant breasts are thin and do not have enough subcutaneous fat to provide adequate tissue for satisfactory mammary enlargement.

Submammary Prosthesis

In regard to the third method of augmentation, that of utilizing plastic substances to build up the size of the breasts, there are now available plastic implants and materials that provide lasting and pleasing cosmetic results. A few years ago when enlargement of the breasts was accomplished by means of plastic sponges, complications were not uncommon. Often the sponge, after being impregnated with scar tissue, became excessively hard. Not infrequently, the contour of the operated breast underwent distortion due to the contracture of scar tissue in the sponge. Furthermore, these sponges occasionally acted as foreign bodies which were extruded or had to be removed. The newer plastic materials and implants, however, cannot be invaded by scar tissue and consequently do not tend to become hard and distorted. Some of these prostheses contain a liquid core which gives the breast a normal consistency on palpation. Finally, complications following use of these newer materials are extremely rare, provided that much care is given to asepsis during the surgical insertion of the implant.

Conclusions

There is a widespread desire for well-developed and neatly contoured bosoms in a large segment of our society. However, augmentation mammaplasty should not be an operative technique designed to please the whims of self-centered female exhibitionists, nor is it something intended to dissolve all sorts of personal or marital problems. On the contrary, it is a surgical procedure of much psychologic benefit in properly selected cases, bringing to the patient an inner sense of satisfaction. Although some of the older plastic sponges, when utilized to build up the mammary prominences, can lead to undesirable complications, the newer plastic materials and implants give excellent results in a large percentage of cases and can be recommended with few, if any, reservations.

Gulliver's Travels — Jonathan Swift*

Gulliver — On the Causes of War

"Sometimes the ambitions of princes, who never think they have land or people enough to govern: sometimes the corruption of ministers, who engage their master in a war in order to stifle or divert the clamour of the subjects against their evil administration. Difference in opinions hath cost many millions of lives: for instance whether flesh be bread, or bread be flesh: whether the juice of a certain berry be blood or wine . . . Neither are any wars so furious and bloody, or of so long continuance, as those occasioned by difference in opinion, especially if it be in things indifferent.

"Sometimes the quarrel between two princes is to decide which of them shall dispossess a third of his dominions, where neither of them pretend to any right. Sometimes one prince quarreleth with another for fear the other should quarrel with him. Sometimes a war is entered upon, because the enemy is too strong, and sometimes because he is too weak. Sometimes our neighbors want the things which we have, or have the things which we want; and we both fight, till they take ours or give us theirs."

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*See Minnesota Med 49:1550, 1966.

I hate to be a kicker, I always long for peace, But the wheel that does the squeaking is the one that gets the grease. — Josh Billings

IT'S THE LAW

Doctor's Examination and Hospital-Record-History Admissible

Although an examining doctor's opinion as to a patient's condition based on the history of the case as given to him by the patient was inadmissible, because it might be a self-serving declaration, his opinion based on his examination of the patient and her case history shown in the hospital records was admissible, a Texas intermediate appellate court ruled.

The patient had suffered back injuries for which she sought to recover benefits under the Workmen's Compensation Act. The doctor, who examined the patient only for the purpose of testifying for her, stated his opinion that her condition had been caused by the injuries she suffered while at work. On cross-examination, he stated that in giving his opinion he had taken into consideration the history of the case as told to him by the patient. The doctor testified on redirect examination that his opinion, based solely on the patient's hospital records and his examination of her and disregarding the history of the case she gave him, was still the same.

The examining doctor could not state his opinion as to the patient's condition based in part on the history of the case as told to him by the patient because the history might have been merely a self-serving declaration, the court said. His testimony on redirect examination changed the situation, and the opinion stated at that time was admissible, the court ruled.

The compensation insurer argued that the doctor should not have been allowed to take into consideration, in forming his opinion, the case history set forth in the hospital records. The patient gave this history when she entered the hospital for treatment and surgery, a time when her main interest would almost certainly have been to get well and when she would have had very little motive to give a false or questionable case history, the court said. Since the case history was most probably accurate, the examining doctor could take it into consideration in forming his opinion, the court ruled.

Liberty Mutual Insurance Company v. Taylor, 376 S.W.2d 406 (Tex., Feb. 7, 1964)

Green Medicinals*

Herbs for the Liver

Ecclesiasticus said: The Lord hath created medicines out of the earth and a wise man will not abhor them.

Therapeutic herbs for the liver include bogbean, gooseberry, lilac, mandrake, snapdragon, and thistles. For anyone with a taste for gooseberries the following relish can be prepared.

Green Gooseberry Relish

Put into a preserving pan four quarts of green gooseberries, five pounds of brown or white sugar, and a little water. Boil until nearly cooked, then add another five pounds of sugar, a tablespoonful of powdered cloves, the same of powdered cinnamon, and a pint of vinegar, and boil till finished. It should boil three or four hours.—C. F. Leyel: Green Medicine

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*See Minnesota Med 49:1602, 1966.

If a man look sharply and attentively, he shall see Fortune; for though she is blind, she is not invisible. — Bacon

Nonspecific Ulcerative Colitis

Puerperal Disseminated Intravascular Coagulation as a Complication

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A STATE OF hypercoagulability leading to disseminated intravascular coagulation has been stated to exist both in the pregnant patient[1] and in patients with nonspecific ulcerative colitis.[2] We have recently observed a patient who developed nonspecific ulcerative colitis during her pregnancy and later developed disseminated intravascular coagulation during the puerperium.

Report of Case

This 22-year-old Caucasian primipara had previously been in good health. There was no history of previous gastrointestinal illness and no family history of colitis or other gastrointestinal diseases. During the first two trimesters of pregnancy she did well.

Onset of Diarrhea

She subsequently developed intermittently severe diarrhea during the third trimester which responded poorly to symptomatic treatment but was not associated with dehydration, hematochezia or systemic toxicity. The patient entered the hospital in active labor but developed a uterine inertia. She became clinically dehydrated and was given intravenous fluids. Following this the membranes were ruptured artificially, labor resumed, and she delivered a normal female infant. The delivery was without incident and the patient tolerated it well.

Postpartem Course

On the *first postpartum day* she developed an ileus, nausea and vomiting and urinary retention. A Foley catheter was inserted and 850 cc. of urine was obtained.

On the *third postpartum day* abdominal x-rays showed the descending colon to be markedly distended. On the fourth postpartum day she developed diarrhea and a temperature to 102° F. rectally. The diarrhea became severe and the patient rapidly went into an electrolyte imbalance which was treated promptly and energetically. However, the diarrhea continued. Multiple stool examinations were done which failed to reveal any ova, parasites or pathogenic bacteria; but Charcot-Leyden crystals were seen and the stools were positive when tested for blood. On the seventh postpartum day, barium study of the colon was interpreted as showing ulcerative colitis. The patient was started on steroids.

On the *eighth postpartum day* while being ambulated she began dragging her right foot. Shortly after this she had a syncopal episode and became cyanotic and hypotensive. Her shock was treated successfully with vasopressors but the right leg became completely paralyzed. Chest x-ray was normal and EKG. showed only atrial tachycardia. Hemoglobin was 12.4 grams %, LDH 480 units and SGOT 50 units. Subsequently she became completely comatose. Neurological examination showed a right hemiparesis, distention of the veins of the right fundus and a deviation of the head and eyes to the right.

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*Department of Pathology, Midway Hospital.

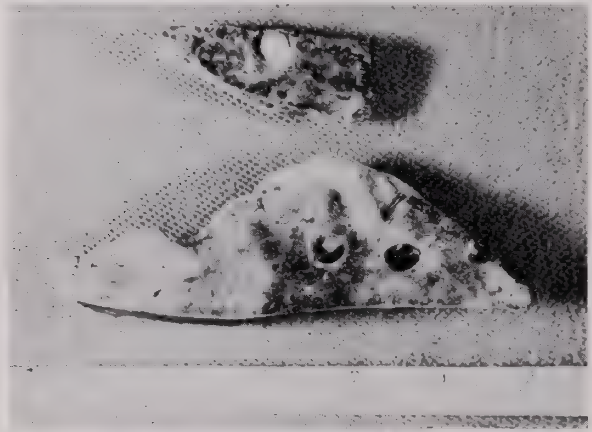
Fig. 1 — Thrombi in branches of hepatic vein with hemorrhagic infarction of liver.

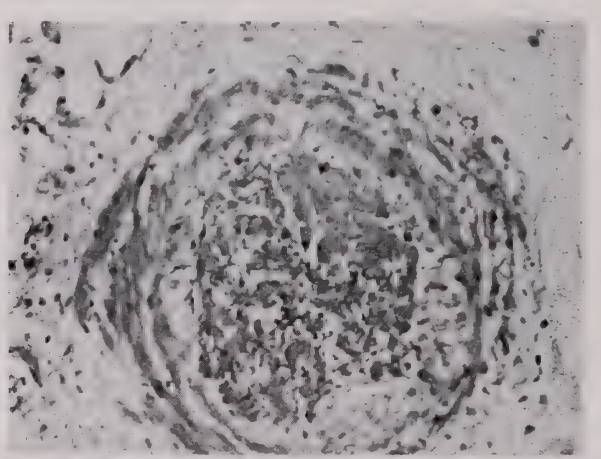
Fig. 2 — Thrombi in small vessels from cervical area (×100).

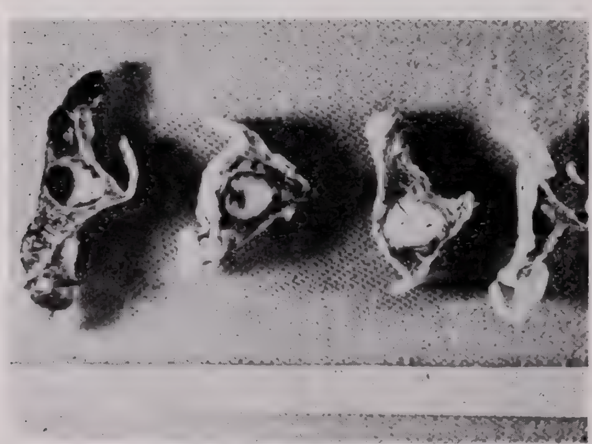
Fig. 3 — Thrombus in superior sagittal sinus.

There was a bilateral positive Hoffman reflex and a positive right Babinski, together with bilateral clonus.

Angiograms

Bilateral carotid angiograms were negative except for the finding of a very slow flow in the cerebral arteries with crossover blood flow into the middle cerebral vessels and filling of the basilar and vertebral vessels. That evening the patient developed seizures. On the tenth postpartum day ventriculograms were done. A very tiny left ventricle was seen on the x-ray films, but no gross shift was noted. A definitely increased cerebrospinal fluid pressure and a softening of the left cerebral hemisphere was also noted at this time. On the eleventh postpartum day the patient developed a thrombophlebitis of the right leg, became increasingly more comatose, and expired on the twelfth postpartum day.

Autopsy Findings

Thrombophlebitis

The significant postmortem findings included a thrombophlebitis of the right leg, a small pulmonary embolus in the right lung, and thrombi in many of the hepatic veins, with hemorrhagic infarction of much of the liver (Figure 1). Thrombi were also present in many of the small blood vessels throughout the body (Figure 2) and a thrombus was present in the left renal artery.

Ulcerative Colitis

Examination of the gastrointestinal tract revealed the typical findings of nonspecific ulcerative colitis involving the terminal ileum and all of the large intestine, with the cecum and ascending colon being more severely involved and the involvement decreasing distally. No uninvolved or "skip" areas were present. The genital organs showed only the findings of the postpartum state.

The Brain

Examination of the brain revealed a complete thrombosis of the sagittal sinus throughout its entirety as well as thrombi in the veins of the right frontoparietal area (Figure 3). A 6 × 3 × 3 cm. area of hemorrhagic infarction was noted in the left frontoparietal area (Figure 4) and smaller scattered areas of hemorrhagic infarction in the right frontoparietal and right occipital areas. Petechial hemorrhages were present throughout the pons, and marked tenting of the cerebellum was noted as evidence of herniation of the cerebellar tonsils. Other findings included an acute benign gastric ulcer and cholelithiasis.

Comment

The evidence for a hypercoagulability state during pregnancy includes the findings of an increase in activity of factors VII, X and fibrinogen plus an increase in factors VIII and IX in certain patients.[1] In addition, decreased fibrinolytic activity has been noted.[3]

It has been postulated, though not proven, that the traumatic event of delivery and separation of the vessels of the placental site may contribute to an augmented coagulability of the blood.[4] The evidence for a hypercoagulability state associated with nonspecific ulcerative colitis includes the finding of an excess of a material similar to factor VIII.[2] In view of the above facts it is interesting that more puerperal patients with nonspecific ulcerative colitis do not have disseminated intravascular coagulation. Possibly this is because most patients with nonspecific ulcerative colitis improve with pregnancy.[5] They may have exacerbations during the puerperium; but presumably there is enough time between delivery and exacerbation so that the hypercoagulability states do not overlap.

Puerperal intravascular coagulation frequently presents as a sagittal sinus thrombosis but may present as pituitary thrombosis (Sheehan's syndrome)* or thrombosis in veins of the extremities or the viscera. The thrombosis occurring in nonspecific ulcerative colitis is usually visceral, pulmonary, or in the extremities; but it may be cerebral as well. The sites of the thrombi are probably determined by local hemodynamics. The sagittal sinus, for example, has ideal conditions for thrombus formation, including slow blood flow and eddy currents caused by some of the posterior cortical veins entering in a direction opposite to the direction of the blood flow in the sinus.

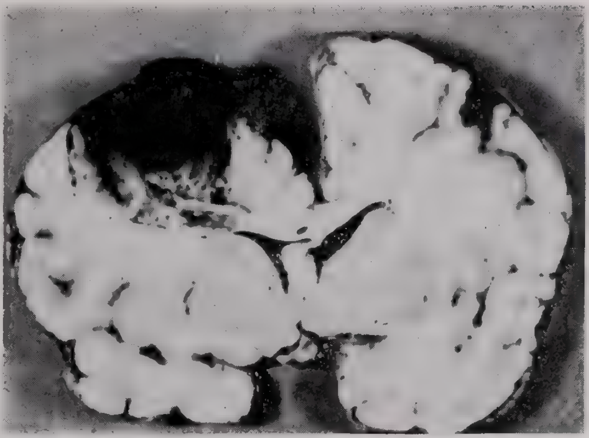

Fig. 4 — Hemorrhagic infarction of left frontoparietal area.

In addition it has been postulated (but never proven) that labor and delivery may cause damage to the walls of the sagittal sinus,[6] as this sinus is affected more frequently in puerperal patients than in others. In view of the above findings pregnant patients with nonspecific ulcerative colitis should be subjected to careful observation during labor, delivery and the puerperium. Dehydration should not be allowed to occur. If any signs of vascular thrombosis occur, they should be vigorously treated. Because of the risk of disseminated intravascular coagulation and a "consumptive coagulopathy" heparinization would seem to be the treatment of choice.

Summary

A case of disseminated intravascular coagulation in a puerperal patient with nonspecific ulcerative colitis is reported. Evidence from the literature suggests that the disseminated intravascular coagulation is due to a state of "hypercoagulability" which is secondary both to the nonspecific ulcerative colitis and to the puerperal state. It is suggested that puerperal patients with nonspecific ulcerative colitis who have severe symptoms during their pregnancy or immediately post partum be watched closely for signs suggestive of intravascular coagulation, especially as evidenced by central nervous system deficits.

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*See page 1694.

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Oliver Wendel Holmes, M.D.

To the Young Practitioner

What shall I say of the personal habits you must form if you wish for success? Temperance is first upon the list. Intemperance in a physician partakes of the guilt of homicide, for the muddled brain may easily make a fatal blunder in a prescription and the unsteady hand transfix an artery in an operation. Tippling doctors have been too common in the history of medicine. Paracelsus was a sot, Radcliffe was much too fond of his glass, and Dr. James Hurlbut of Wethersfield, Connecticut, a famous man in his time, used to drink a square bottle of rum a day, with a corresponding allowance of opium to help steady his nerves.

Sheehan's Syndrome*

(Postpartum Pituitary Necrosis Syndrome)

In 1937 Sheehan emphasized that during pregnancy the pituitary becomes enlarged but that during childbirth, its blood supply becomes diminished and it is particularly susceptible to thrombosis.

If a woman suffers from severe hemorrhage, collapse, or shock at the time of delivery or in the postpartum period, she should be observed for subsequent signs and symptoms indicating pituitary necrosis, which may manifest as a multiglandular deficiency and possibly myxedema. Pallor, asthenia, apathy, atrophy of the breasts with loss of areolar pigment, inhibition of lactation, loss of pubic and axillary hair, and genital atrophy are most of the presenting signs. Amenorrhea may be temporary or permanent. Hypoglycemia is usually found and may be sufficient to produce severe symptoms.

Treatment should be directed to the polyglandular deficiency and failure. If the syndrome is not recognized and substitution therapy not instituted, death may occur.

Durham, Robert H. — Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

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*See page 1693.

On Quaffing

If you are loose in your ways you won't improve them by getting tight. — The Schemer

Skin Replacement on the Extremities*

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OCCASIONALLY FOLLOWING the extensive losses of tissue on the extremities, associated with automobile, industrial or thermal accidents, coverage of the exposed area is necessary to obtain healing of the wound.

Free Skin Grafts

In the avulsion type accident, where skin and subcutaneous tissue are lost, the wound may often be debrided and a split-thickness graft applied immediately to close it. If after debridement, however, there is still tissue of questionable viability, it is better to dress the wound for several days until a satisfactory granulation bed is present.

Temporary Graft

Coverage of extensively exposed tissue of the hand, wrist, ankle or foot with thin free grafts may be a temporary though important step in the final repair.[3] With considerable loss of skin and underlying tissue, fixation of tendon or joints in the dense scar often occurs. Occasionally, after allowing a scar to soften for several months, function of the contracted member can be improved by release of the constricting scar and application of a thick graft to the skin defect.[1]

Protection of the Graft

Elevation of the leg is most essential during the postoperative period in order to reduce fluid accumulation under the graft. After the graft has become adherent with primary healing, it must be protected by elevation of the resting extremity and supported by the use of an elastic bandage when the leg is in a dependent position. Such an elastic support should be worn from three to six months postoperatively. If elastic support is not worn, the stasis may result in cyanosis, blistering and loss of the graft. Healed free grafts have reduced sensation, are fragile, and should be protected. This includes cleanliness and avoidance of injury from work or poorly fitting shoes. The patient may be able to wear a larger soft shoe or one with wool fleece-lining to minimize rubbing on the graft. Special attention should be given to possible blistering of the graft if one-day-a-year sports such as skating or hunting are indulged in. Free grafts have a wider area of usefulness for children than for adults who require a pedicle flap.[7]

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*Presented at the Minneapolis Surgical Society meeting May 3, 1965.

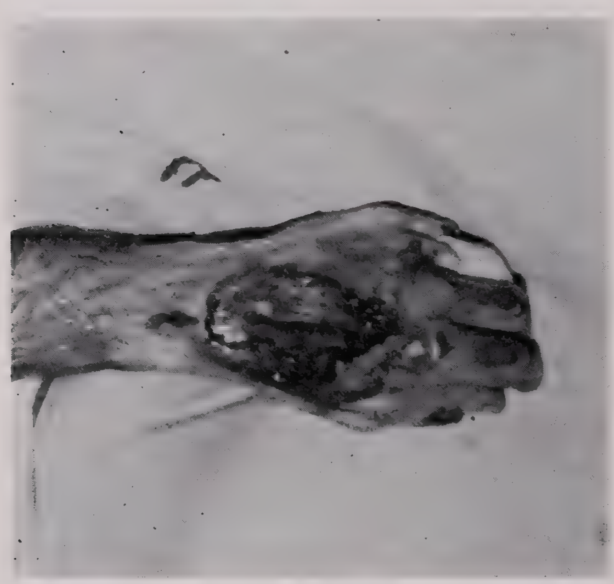

Fig. 1-a — Grinding wheel injury to dorsum of left hand and thumb. Photograph a few hours after injury. There is loss of skin, subcutaneous tissue and paratenon with tendon bare across base of wound.

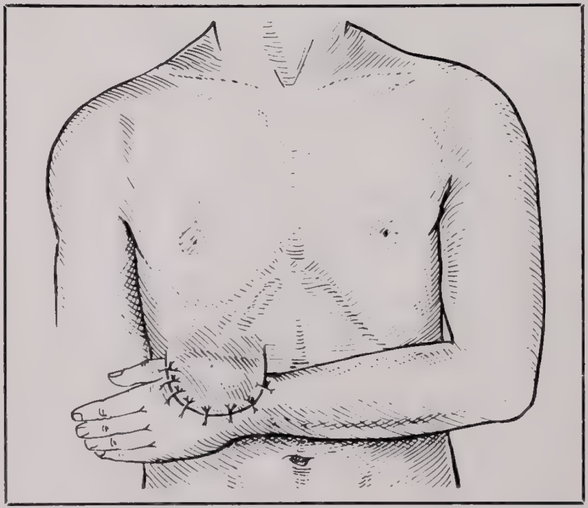

Fig. 1-b — Following debridement, an abdominal pedicle flap was elevated and sutured over the left hand wound. A free skin graft was applied to the abdominal wall defect. The pedicle flap was severed from the abdomen in two stages with final detachment after 25 days.

Pedicle Skin Grafts

Free skin grafts alone are often not satisfactory; what is required is excision of the scarred area and coverage of the resulting defect with a thick pad of durable skin and subcutaneous fat attached to a pedicle. After the area has been covered with nonscarred skin, future reconstructive features such as tenolysis, tendon grafts, nerve grafts or bone surgery can be carried out with better expectation of improvement.

Elective Procedure

Generally speaking, pedicle flaps are performed as elective procedures after the original wound has healed by secondary epithelization or by free grafts. Following the healing and control of the local infection, and perhaps after a period of appropriate splinting or physiotherapy, the definitive reconstruction can be planned and a pedicle flap used to provide durable skin to cover the involved area.

Upper Extremity Pedicle

A local rotation or sliding flap may occasionally be used for small upper extremity defects; often, however, the large size of the defect precludes use of the pedicle flap

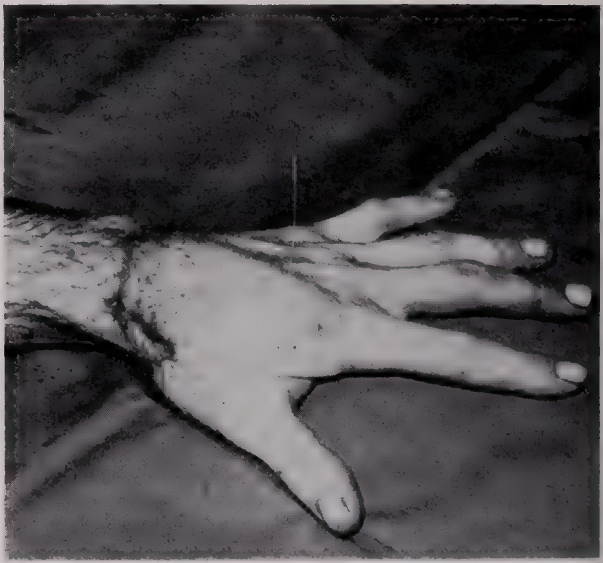

Fig. 1-c — Photograph 11 months after injury. There is normal function of the thumb and index finger.

adjacent to the defect. For upper extremity reconstruction, a source of relatively hairless skin can be found on the anterior chest or abdominal wall. Tube pedicle flaps are ideal; but often a quicker, more satisfactory reconstruction can be accomplished with an open flap.[4] The flap must be patterned so that it will be adequate in size, with attention directed to preserving the inflow and outflow vessels. If the base of the pedicle is narrow in relation to its length, elevation is more safely carried out in stages about one week apart. Following complete elevation, if the flap circulation is satisfactory, the recipient defect can be freshly excised and the flap skin sutured over the defect. The area from which the flap is raised and the exposed part of the undersurface of the flap should be covered with a free skin graft. Following flap approximation to the extremity, extensive taping will usually provide required immobilization to prevent disruption during movement or sleep. The flap will usually receive its new vascular supply in three to four weeks, and severance of the nourishing pedicle is then possible.

Lower Extremity Pedicle

Lower extremity pedicle flap repairs usually require several operative steps for their completion. For this reason, pedicle flaps are seldom recommended for areas which are open and locally infected, when the wound can be temporarily healed with free grafts.[2] In the lower leg and foot, there is usually little opportunity to use an adjacent sliding

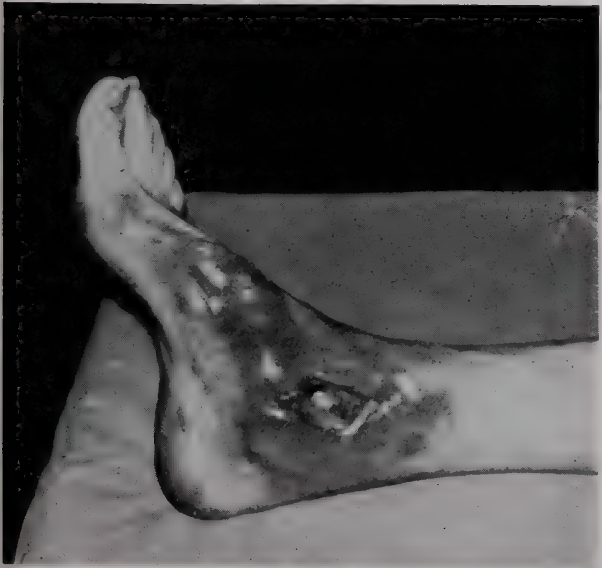

Fig. 2-a — Old post-traumatic injury to the right foot and ankle region. There has been breakdown of the previously skin-grafted area and there is exposure of the ankle joint.

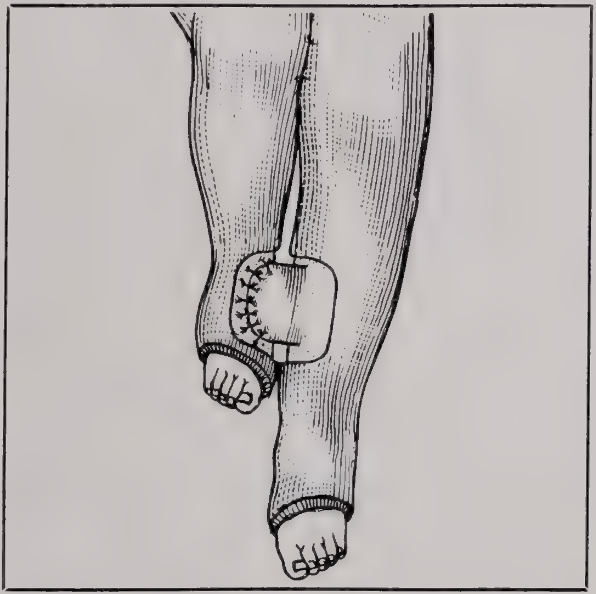

Fig. 2-b — A pedicle skin flap was prepared on the opposite calf by gradual elevation of the flap in stages (delaying procedure). The thin atrophic skin and the ulcer on the right foot were excised. The pedicle flap was sutured to the defect and the casts positioned and held to prevent tension on the pedicle. The flap was detached from the calf and fitted to the foot defect five weeks later.

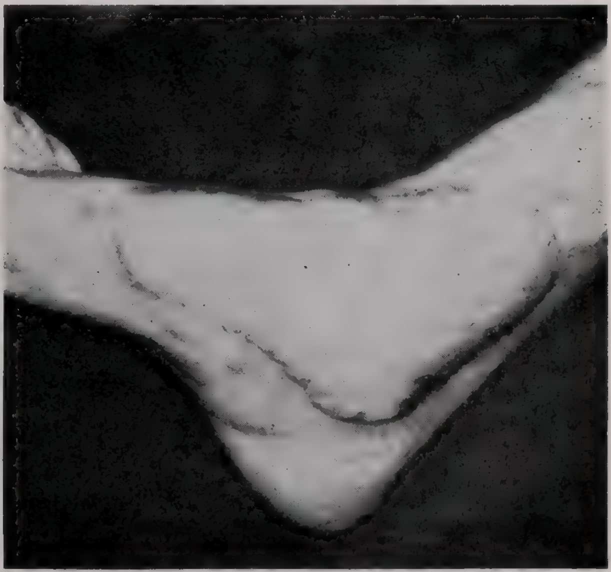

Fig. 2-c — Photograph of right foot 14 months after cross-leg flap procedure. There is normal ankle motion and no destruction of the ankle joint. The area has remained healed and the overlying pedicle flap skin has tolerated minor injuries of daily work.

or rotation flap. Therefore, the required thick pad of skin must be obtained from a less important area on the body (a calf — cross-leg flap; a thigh-cross thigh flap; a flap from abdomen via a wrist carrier). These procedures are exacting; each step must be carried out in detail. Whereas an abdominal flap may often be elevated and transferred to the hand primarily, the necessary dimensions and direction of a calf pedicle in a cross-leg flap procedure may preclude this. The circulation from the edges and undersurface of the flap must be cut off gradually over a period of weeks, redirecting the circulation all through the hinge. After these initial preparatory delaying procedures, the flap can be elevated entirely, as it should then have a satisfactory circulation to tolerate transferring it to the defect on the opposite lower extremity. Tension on the transferred flap is prevented by holding the legs attached to each other with well padded casts. The pedicle is maintained in this position for four or five weeks for the skin to receive vascularization from the foot[5,6] so that gradual cutting off of the nourishing pedicle can be carried out (Figure 2-b).

Pedicle for Exposed Bone, Fractures and Joints

If there is tissue loss over a bone or over a compound fracture, and if periosteum is still present, granulation will cover the area and it can be closed with a free graft. If periosteum is destroyed and granulations do not grow over the bone, drill holes or decortication of the bone may be necessary before granulation will emerge. In the lower third of the tibia this set of circumstances often leads to nonunion of the tibial fracture and the thin atrophic skin or graft immediately overlying the fracture site. Here a thick pad of skin will probably be required prior to bone grafting the tibia. Open joints may be impossible to close by any free graft or local flap. Hence a pedicle flap may have to be applied directly over the open joint or an infected wound in order to obtain closure.

Flap Coverage

On occasions an injury will exist which is very deep and involves important structures but which is localized to a small area and can be converted to a relatively clean surgical wound. If the periosteum or paratenon is lost or a joint is exposed, immediate closure of the wound is desirable but can not be accomplished with a free graft. If such a wound can be closed by a flap, fixation or loss of exposed tendons can be avoided.

Undermining the edges of the wound or use of a local rotation or sliding flap is simplest. However, on the extremities there is often not enough adjacent skin to be advanced across small defects. A pedicle flap elevated immediately from the anterior abdominal or chest wall may be used to cover small upper extremity losses, but such application must be used only with consideration of the eventual reconstruction. Immediate flap repairs can occasionally be employed safely in the thigh or leg but rarely should be used for defects at the ankle or foot.

In a hand with deep injuries about the proximal or middle joints the intricate extensor mechanism may be so badly damaged that obtaining a functioning finger is impossible. Occasionally this useless, numb finger can be used as a flap by filleting out the bones and tendons and utilizing the skin as a perfectly vascularized local pedicle flap to provide skin in a scarred contracted area. This is particularly true in the web space between a thumb and the first opposable finger. Likewise, in an acute hand injury the skin from a finger which cannot be salvaged can often be used to cover adjacent areas of lost tissue. The filleted toe may likewise be useful for local skin coverage.

Postoperative Care

After a skin flap is successfully transferred to the upper or lower extremity, it must be gently supported for several months with elastic dressings and protected from stasis with periods of elevation; in addition, the transferred skin has reduced sensation and must be guarded from injury. The limb with the successfully transferred flap must have the same meticulous care as a free graft. After several months the successfully transferred flap becomes more durable and will tolerate reconstructive procedures, removal of excessive underlying fat and tailoring of the skin edges.

Limitations of Pedicle Flaps

If prolonged immobilization of the area is required, these procedures may not be applicable in the very young child or the elderly arthritic patient. The long period of cast immobilization of lower extremities is poorly tolerated in patients past 55 years of age, in arthritics, or in patients with obliterative vascular disease, lower extremity venous disease or neuropathy.

In contrast, pedicle flaps in the upper and lower extremities of young healthy persons can be transferred quite rapidly and safely. In this type of patient a pedicle flap is satisfactory for covering areas about the hand, the lower leg or the foot, which would otherwise be unstable and undergo repeated ulceration.

Conclusions

Some useful reparative surgical procedures for traumatic soft tissue losses of the hand, leg and foot are presented. Where possible, the wounds should be initially healed by free grafts or epithelization. If free skin graft repairs are unstable, a pedicle flap of skin to cover the defect may be useful. The use of local and more distant pedicle flaps in the upper and lower extremity is presented.

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Dr. Benjamin Winslow Dudley

The Lexington Intelligencer, December 9, 1836, considered Dr. Benjamin Winslow Dudley, of the Transylvania Medical College, the first surgeon in the West to remove a cataract of the eye. During his long surgical career he was said to have made over two hundred lithotomies with only four per cent mortality; more than one hundred of these were done before a single death was recorded. The Kentucky Gazette for April 11, 1827, reported three lithotomies performed by him in one day. Dr. Dudley also successfully ligated the subclavian artery for axillary aneurysm in 1841. In 1828 he published a report of five successful cases in which he had trephined the skull for the relief of epilepsy due to pressure on the brain. He was probably the first surgeon in the United States to perform this operation. Dr. Dudley was among the first doctors of the Middle West to discard the lancet; the stress which he laid upon the use of boiled or boiling water in surgery at that early time is worthy of comment. He emphasized preparatory treatment, to which he was more inclined to attribute his success than to his superior skill.*

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*Pickard and Buley: The Midwest Pioneer, Henry Schuman, New York, 1946.

Some people are always grumbling because roses have thorns. I am thankful that thorns have roses. — Alphonse Karr

Music and Medicine

Maladies of Musicians

As early as 1700 Ramazzini, who studied occupational diseases, stated that singers and wind-instrument players were subject to hernia and to hemorrhages in the chest. During the eighteenth and nineteenth centuries other observers' notes and records resulted in a more inclusive and comprehensive assessment of diseases peculiar to vocalists and instrumentalists.

"The professional musician uses only skilled methods in producing sounds; these methods entail a continual drain on his physical and mental abilities, and illnesses often result which are peculiar to his profession. *Nervous exhaustion,* for example, caused by a muscle spasm in neuromuscular fatique, will appear in the pianist and in the drummer. *Emphysema* of the lung is seen in both the singer and the hornblower. *Muscle fatigue* and finger sores arising from pressure on the cutaneous tips of the fingers are common to the guitar player. The hornblower may have a *hypertrophy of the abdominal muscles,* which can result in a relaxed abdominal wall. *Muscle spasms* or cramps occur at the area of the nerve endings in the fingers of pianists and organists. Zither players have the same *neuro-muscular spasms* and hypersensitivity in the left hand. In string players, especially violinists, spasms are frequent in the left thumb and forefinger and the right thumb and forefinger. The flute player may develop a spasm of all the fingers, the drummer one of the thumb and wrist, the violinist one of the right deltoid muscle because of the elevation of the bow. Hornblowers have muscle spasms of the lips and tongue muscles; singers suffer from various muscle strains. Harp players may develop spastic muscles of the legs from holding the harp between the legs. Even the director is not immune; he may have a mild spasm of the shoulder and right arm muscles. In addition there is apt to be generalized fatigue of the eyes and ears and central nervous system of all musicians when they have been musically active for a time."*

Some revealing articles in older medical journals provide specific focus on a few such disorders. For example, a monograph, *Vitiligo of Upper Lip in Players of Wind Instruments,* appeared in a 1943 issue of Archives of Dermatology; in 1885 one issue of the British Medical Journal included a discourse, *Digital Tenotomy in Pianists;* an 1899 issue of the International Clinician presented a treatise, *Indurated Sore of Lower Lip in a Cornetist;* and the Memphis Medical Monthly in an 1899 issue contained an article, *Chorditis Tuberose, or Singer's Nodule, Some Desultory Remarks Thereupon.*

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*Music and Medicine, Edited by D. M. Schullian and Max Schoen.

Micro-adults

Children are not simply micro-adults, but have their own specific problems. — Bela Schick

Spontaneous Rupture of the Splenic Artery

Probably Due to Aneurysm

ARNOLD O. SWENSON, M.D.
JOHN M. RUNQUIST, M.D.
Duluth, Minnesota

SPONTANEOUS RUPTURE of the splenic artery during pregnancy, probably due to aneurysm, is a rarity,[1,2] and this case is added to the fewer than thirty cases which have been reported in the literature to the present time.

Rupture of an aneurysm of the splenic artery, or traumatic rupture of the spleen, is a serious complication, particularly when associated with pregnancy. The fortuitous* outcome of this case is undoubtedly due to prompt surgical intervention and blood replacement.

Case Report

This 28-year-old white female, gravida VIII, para VII, in her 36th week of pregnancy, was admitted to St. Luke's Hospital on February 15th of this year. She gave a history of developing an acute pain in the epigastrium and in the left flank while bending over emptying the lower shelf of the refrigerator. The pain was so severe that she fainted, but she recovered consciousness shortly afterwards and was able to go to the telephone and summon help. She denied any trauma associated with this onset of pain.

Her chief complaint on admission was severe pain in the epigastrium and below the left costal margin, and she was much more comfortable lying on her right side.

Her past history was essentially negative except for her pregnancies, all of which had been relatively normal, with uncomplicated delivery of seven term children. Her present pregnancy had been relatively normal, with no elevation in blood pressure. Urinalyses had been normal. She had been treated for a mild secondary anemia, which responded to iron therapy.

Physical and Laboratory Findings

Her blood pressure was 110 systolic, 70 diastolic; her pulse was 72 and her temperature 97.6°. The hemoglobin on admission was 9.8 gm. and the white count was 17,500. Serum amylase on admission was reported as 32 units. Her total serum bilirubin was .8, with the direct bilirubin .25 and the indirect .55. Urinalysis was normal.

Fetal heart tones were present but rather indistinct; the upper abdomen seemed to be mildly distended, with slight rebound tenderness. The uterine musculature appeared much firmer than usual.

Progress

She was given 50 mg. of demerol for relief of pain, and for the next four hours she was observed carefully in the obstetrical suite. About four hours later, while being examined by one of us, she suddenly went into acute shock. Her blood pressure dropped from 112/72 to 56/0. Her pulse was imperceptible and the fetal heart tones disappeared. She was given a unit of plasma followed by two units of blood when it became available. It was felt at that time that we were dealing with an abruptio placentae, as the uterus seemed to become quite distended and very hard, and with the disappearance of the fetal heart tones it seemed that we were dealing with retroplacental hemorrhage.

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*See Test Your Word Score Page 1719.

Operative Findings and Procedures

The patient was taken immediately to the operating room and a laparotomy was performed. On opening the abdomen through a midline incision at the level of the umbilicus, about 2000 cc. of blood was found in the abdominal cavity. The source of the bleeding was not immediately determined because of the size of the uterus. The uterus was opened through a classical section incision and a stillborn fetus delivered. There was no retroplacental hemorrhage, although there was evidence of placental separation.

The wound in the uterus was rapidly closed, and with the decrease in the size of the uterus the abdomen could then be explored. The hemorrhage was found to be coming from the splenic pedicle, and there was no evidence of rupture of the spleen or laceration of the capsule.

A splenectomy was done as rapidly as possible. The original incision was extended about two inches above the umbilicus. The surgical procedure was not too difficult because of the relaxation of the abdominal wall following the decrease in size of the uterus. The splenic pedicle was clamped and the spleen was removed. The splenic pedicle was infiltrated with blood and it was apparent that the original bleeding had occurred into the lesser omental cavity, as considerable blood had infiltrated into the gastrocolic omentum and even into the omental layers.

The splenic pedicle was tied en masse with No. 2 chromic catgut, and then the vena brevia were ligated separately. Following irrigation of the peritoneal cavity the abdomen was closed.

The patient received a total of 3500 cc. of blood, 250 cc. of plasma, and another 200 cc. of dextran. She made an afebrile, uneventful recovery, and was discharged on her ninth hospital day. She was readmitted a week later with evidence of embolic phenomena in the left chest, which responded to therapy normally, and she was discharged five days later in good condition.

Pathologic Findings

A stillborn fetus weighed 6# 8 oz. and showed no abnormality. The placenta was not abnormal. The spleen weighed 240 gm., measured 4½ × 9 × 5 cm., and showed evidence of chronic passive congestion. There was a hemorrhagic area in the hilus which apparently resulted from the blood dissecting upward from the pedicle.

Discussion

As is frequently true in cases where the spleen is removed as an emergency procedure, no evidence of aneurysm could be documented. In most of the cases where an aneurysm of the splenic artery has ruptured, the aneurysm has been demonstrated at post-mortem examination. I am sure that if an aneurysm was present in this case, such evidence was destroyed by clamping the pedicle and removing the spleen.

A. J. Tomsykoski et al.,[3] reporting in the American Journal of Obstetrics and Gynecology in December 1953, summarized 28 cases of aneurysm of the splenic artery associated with pregnancy. Out of 28 patients, only two survived; in both instances survival was due to prompt surgery. There were two fetal survivals.

The symptom complex of epigastric and left upper quadrant pain was present in all the cases reported, and in none of the 28 cases was the true diagnosis made. Usually, rupture of the uterus, premature separation of the placenta, or other catastrophes related to ruptured viscus, was the diagnosis made. The incidence of traumatic rupture of the spleen[4] is now rising, due to the number of automobile accidents that occur, and pregnancy is a complicating factor in the treatment of the injury.

Lyons et al.,[4] of Mt. Sinai Hospital, reported 28 cases of rupture of the spleen. There were 15 deaths, the first eight of these reported before 1880. Excluding these fatalities, there were seven deaths in 20 cases. Further analysis of the 28 cases showed that of 16 patients operated upon, three died. All seven of the patients with traumatic rupture were operated upon and all recovered.

It is evident from the above report that early diagnosis of an acute abdominal emergency with early surgical intervention is essential if we are to save the patient's life. Careful observance of blood pressure and evidence of falling hemoglobin are serious warning signals, and adequate blood replacement is essential in the surgical treatment.

The maternal mortality rate has been high in the earlier cases reported but should markedly decrease with earlier surgery and adequate blood transfusion.

Conclusions

A ruptured splenic artery at the pedicle, probably associated with an aneurysm treated by early surgery and adequate blood replacement is essential for a successful outcome of this emergent situation. The outlook for the fetus remains grave due to the period of anoxia that invariably will occur as the result of hypotension. Awareness of the fact that acute surgical emergencies can occur in late pregnancies not associated with the pregnancy itself will contribute greatly to the successful outcome in the treatment of these cases.

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WHAT'S YOUR DIAGNOSIS?

A 29-year-old right-handed man was in excellent health until four weeks prior to hospitalization when stiff neck and occipital headache developed. These symptoms would be present for two to three hours, would subside, and would recur approximately three times a week. Two weeks later unsteadiness in walking developed with a tendency to fall to the right. One week prior to his hospitalization nausea and vomiting developed.

On his admission to the hospital, his temperature was 100.2° F., blood pressure 128/80 mm. of mercury, and pulse 72 and regular. No abnormality of the cranial nerves was found except for bilateral early papilledema. There was no nystagmus. He did not have a stiff neck. He had generalized hyperreflexia, but the toes turned down on plantar stimulation. Results of the finger-nose and heel-knee tests showed evidence of moderately severe cerebellar ataxia on the right and a minimal amount of cerebellar ataxia on the left. There was some hypotonia on the right.

The hemoglobin measured 14.7 gm.; leukocytes numbered 6500 with a normal differential cell count. Roentgenograms of the cervical portion of the spinal column and of the head did not show evidence of any abnormality. An electroencephalogram showed delta waves, grade 1 biparietal occipital, maximal on the left, and generalized dysrhythmia, grade 2. Special contrast studies were then performed by a neurosurgeon.

What's Your Diagnosis? Turn to page 1707.

Requisites

Medical Practice is not knitting and weaving and the labor of the hands, but it must be inspired with soul and be filled with understanding and equipped with the gift of keen observation; these, together with accurate scientific knowledge, are the indispensable requisites for proficient medical practice. — Maimonides (1135-1204)

Drive Safely

If you want to live to see ninety, don't keep looking for it on the speedometer.

— Look-out

Home Remedies of the Frontier*

During the larger part of the early life of Minnesota as a territory and a state, those on the frontier made their own medicine. There were no doctors or pharmacists nearby. People who were sick relied upon their own strong constitutions and the medicines that they could make from the materials around about them.

* * *

The Indians knew much about the curative properties of many growing things.

The Chippewas learned that the pitch of the balsam fir would help a headache. The umbrella plant was applied as a poultice for a sprain, and wild sarsaparilla was good for the blood. When a Chippewa chief had trouble with his eyes he sent the squaw out for the jack-in-the-pulpit and dogwood. Wild ginger was good for a pain in the stomach and the fern helped relieve bites, of which there were many.

The moccasin flower, later to become Minnesota's state flower, had something about it that would help a toothache. Fireweed was good for bruises and goldenrod was excellent for pain in the Redman's chest. Tamarack was used for burns and white spruce gum would help loosen a stiff joint. The plum had some disinfecting qualities and the blackberry helped a cough.

* * *

The frontier of the white man also had its remedies, some of which may have been learned from the Indians. Others had been handed down from generation unto generation and many of the things used in the earliest days in New England were found helpful, generations later, on the Minnesota homesteads.

Ginger, which the Indians found good for an inside pain, was a favorite remedy in the frontier home. Plenty of good red pepper with hot water was considered excellent for almost anything. Sweet flag, from the edge of a nearby swamp, was a good astringent. Pennyroyal was a standby. Sulphur and molasses made an effective, but not well liked, remedy for many ills.

The responsibility of making up the home remedies was usually left to some older member of the family, a grandmother if there was one around. When she noticed the peaked look and the spring lagging in the children she might put together a combination of yellow dock, black alder, burdock root, sassafras bark and wintergreen. This would be stewed on the back of the stove to make a drink which tasted bad enough to cure anything.

* * *

Anyone with any kind of ailment could get hope out of the early day newspaper. There was no lack of enthusiasm in the claims for what a bottle or a pill would do.

In the first issue of Minnesota's first newspaper, more than three columns of space were given to drug and medical advertising. Especially prominent were the claims for the goodness of Sloan's preparations for both man and beast. Not only did Sloan have a liniment for horses but he had an application for human beings that was especially effective for sprains, bruises, cuts, burns, chilblains, ulcers, pain-in-the-back and rattlesnake bites. Coxe's Hive Syrup, Stoughton's Bitters, and Thompson's Eye Water were evidently current favorites.

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*From North Western Druggist — July 1949.

Computer Medicine

Its Application Today and Tomorrow*

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THE ADVENT OF automation and computers will undoubtedly introduce a new era of medical practice. It is predictable that the computer probably will have the greatest technological impact on medical science since the invention of the microscope. The combination of automation and computers is already producing complex systems with speed and precision unmatched by even the most highly trained personnel: systems which can tirelessly perform routine repetitive procedures day after day, faster, more accurately, and in a manner not humanly practical, nor even possible.

Cybernated† systems, those combining automated equipment with computers utilizing on-line communications, are already being applied in the practice of medicine. The introduction of a cybernated system not only speeds up the quantity of work, improves the quality and lowers the cost, but usually produces changes in thinking and philosophy relative to the functional aspects of the work. For example, the introduction of a large automated chemical analyzer system coupled with electronic data processing has not only permitted us to perform laboratory tests faster, more accurately, and at a lower unit cost, but suggested that perhaps a broad profile of laboratory tests might be beneficially provided routinely to all patients, rather than the traditional teaching and practice of ordering only a limited number of tests for specific clinical indications. The advent of cybernated systems will permit mass production of more data on more people and also more data on each individual person. This will make feasible more explicit evaluation of medical care and also more accurate appraisal of one's biophysico-chemical individuality. One can reasonably predict that within ten years every hospital will have or will be participating in some cybernated systems.

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Paper presented at the 113th Annual Meeting of the Minnesota Medical Association, Saint Paul, Minnesota, May 16, 1966.

**Director, Medical Methods Research, The Permanente Medical Group.

†See Test Your Word Score Page 1719.

An example of a cybernated system in operation today in an outpatient department is that being provided in the San Francisco Bay Area to members of the Kaiser Foundation Health Plan. This Multiphasic Health Checkup, as it is called, is now being received by 40,000 adults each year. The entire Checkup consists of three parts: (1) the Automated Multiphasic Screening Program (a battery of tests and procedures); (2) a physical examination by an internist; and (3) a group of specialty physician examinations, including a gynecological examination (with cervical smear for cancer detection) and a sigmoidoscopy.

Automated Screening Program

The testing period of the Automated Multiphasic Screening Program takes two to three hours and includes the following:

1. Electrocardiogram (6 leads) simultaneously graphed on paper by a direct recording, multiple channel Sanborn optical oscillograph.
2. Chest x-ray (70 mm. minifilm).
3. Breast x-ray (cephalocaudal and lateral views in women over age 45).
4. Weight and skinfolds; height and other body measurements recorded by an automated anthropometer with direct punched card output.
5. Pulse and blood pressure recorded supine.
6. Visual acuity (modified Sloan chart) and pupillary escape test (an unsustained pupillary light reflex occurring in retinal or optic nerve disease).
7. Ocular tension (measured by Schiotz tonometer).
8. Retinal photograph (of right eye).
9. Forced expiratory vital capacity (1 sec., 2 sec. and total) and peak flow by the Wedge spirometer.
10. Pain reaction test (a modified Libman test measured as pain tolerance to increasing pressure on Achilles tendon).
11. Hearing test (for six frequencies by a Rudmose-Bekesy automated audiometer).
12. Self-administered health questionnaire forms (present and past history). In addition, a set of 207 medical questions on prepunched cards are sorted by the patient so that the "yes" responses can be automatically reproduced for computer processing.
13. Psychological questionnaire test with 155 questions sorted by the patient in a manner identical to (12) above.
14. Tetanus toxoid immunization (with Hypospray gun).
15. Blood chemistries performed within 12 minutes by a multichannel technicon AutoAnalyzer with direct punch card output, including: (a) Serum glucose (one hour after 75 gm. glucose orally), (b) Serum creatinine, (c) Serum albumin, (d) Serum total protein, (e) Serum cholesterol, (f) Serum uric acid, (g) Serum calcium, (h) Serum transaminase (SGOT).
16. Blood hemoglobin and white cell count automatically measured.
17. Blood group (ABO).
18. Serological (VDRL) test for syphilis.
19. Blood rheumatoid factor (latex fixation slide test).
20. Urinalysis for: (a) Urine pH, glucose, protein, and blood (paper strip) tests. (b) Urine bacteria (six-hour triphenyltetrazolium chloride culture of midstream specimen).
21. Automated multiphasic screening is completed and, in accordance with programmed "advice" rules, additional tests are arranged by means of an IBM 1440 computer, including return appointments for physicians. A summary report printout is provided to the physician before the time of his appointment with the patient. If the patient has certain combinations of symptoms and test values which fulfill the criteria for selected diagnostic categories, it is suggested that the physician consider these diagnoses.
23. The physician reviews the summary report at the time of the patient's office visits, directs further history toward elaborating upon the questions to which the patient has answered "yes," and to the reported test abnormalities. He completes his physical ex-

amination and communicates back to the computer by recording his findings and the patient's final diagnoses on a form which is processed through an optical reader and stored in the computer.

The Future

In the next five years it is likely that:

1. The electrocardiogram, the phonocardiogram, the blood pressure, and the respirogram will all be automatically read "on-line" by the computer.

2. Considerable progress will be made in the machine interpretation of roentgenograms.

3. Self-administered programmed questionnaires communicating directly with the computer will permit extensive history taking, utilizing "branching" questions. For example, if the patient answers "yes" to a general question, then the next question will branch into more detailed exploration of specific sub-systems.

4. Automated laboratory equipment will permit simultaneous analyses of 40 or more tests with continual "on-line" quality control monitoring by the computer.

5. Most data will be subjected to extensive processing and analyses before being presented to the physician to save his time. The computer will suggest to the physician likely diagnoses to be considered, with estimates as to the probable accuracy of these diagnoses as expressed in terms of sensitivity and specificity. As the complexity of the information increases and we supply more complex analyses, indices and profiles on patients, it will require more physician judgment, not less, to make optimal decisions how best to utilize the information for advice and treatment in accordance with the behavior and personality of the individual patient.

Conclusions

The physician who is skilled in diagnostic evaluation of the complex physiological systems of the human body is probably the best-trained systems analyst in present society. Once cybernated systems applicable to medical science become generally available, the practicing physician will not only readily accept and adjust to them, but will soon demand these services for his patients. In the future, it is likely that every community of 100,000 or more will have affiliated with one of its larger hospitals an automated multitest laboratory, which will be available for admission examinations and preoperative examinations for the hospital patients, and which will be utilized for office patients for periodic health examinations, general health examinations for special purposes (industrial, insurance, etc.), early sickness consultations and diagnostic surveys. These multitest laboratories will undoubtedly be affiliated with a regional computer center which will provide data processing services through connecting telephone lines.

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ANSWER TO WHAT'S YOUR DIAGNOSIS

(From page 1703)

Ventriculography showed dilation of the entire ventricular system down to the middle of the aqueduct, which was displaced upward and forward by a mass in the posterior fossa.

Suboccipital craniectomy was performed. When the dura was opened the cerebellar tonsils were found to be herniated through the foramen magnum, on the right more so than on the left. A large cystic hemangioendothelioma was found in the right cerebellar lobe.

Photographic Contest

The Editors of MINNESOTA MEDICINE, in collaboration with the Doctors' Photographic Society of Minneapolis, take pleasure in announcing a monthly photographic contest. The contest is to promote an interest in photography in the medical profession. First prize each month will be publication in full color of the winning picture in MINNESOTA MEDICINE.

The following rules will govern the conduct of the contest:

1. Only doctors of medicine are eligible to submit pictures, and the picture must have been taken or composed by a physician.
2. Each contestant may submit not more than two pictures each month.
3. Only color transparencies, 35 mm. to 2¼″, can be considered.
4. Each slide should be labeled with the maker's name, address, and the identifying title.
5. Slides should not be mounted on glass, but can be protected in plastic sleeves or envelopes.
6. Each entry must be accompanied by a self-addressed, stamped envelope if return of the picture is desired. Returns will be made shortly after the close of the contest each month. The winning photograph will be retained but will be returned after it has been used.
7. The deadline date for entry will be the 10th of each month and the winner of each month's contest will be announced in MINNESOTA MEDICINE in the subsequent issue. The date of publication will be three to six months in advance.
8. There will be no limitation on subject material except as indicated in item 10.
9. Model releases will be requested of winners where appropriate.
10. Judges will be selected by the editors of MINNESOTA MEDICINE and the Doctors' Photographic Society. The judges will be guided by the precepts of the Photographic Society of America, and winners will be based on appropriateness, interest, impact, and technical excellence.
11. The editors of MINNESOTA MEDICINE and the Doctors' Photographic Society cannot be responsible for entries lost or damaged, but every effort will be made to protect submitted pictures.

Your pictures are hereby invited. Please submit pictures to:

Photo Contest Editor
MINNESOTA MEDICINE

Editorials

Estimation of the Rate of Cholesterol Synthesis in Patients

IN RECENT YEARS there has been considerable interest in determining the effect of various cholesterol-lowering methods on cholesterol synthesis. In some instances, estimates of "synthesis rates" with a given regimen have been contradictory. For instance, in the case of large doses of nicotinic acid, studies in animals have indicated an increase,[1] a decrease,[2] and no change[3] in the rate of cholesterol synthesis. Such discrepancies have led to questions about the precision of the methods used in quantitating cholesterol synthesis.

Most workers in this field have used radioisotopes in their studies. The nature of radioisotopes requires the use of a number of basic assumptions in the calculation of synthesis rates from the data obtained. In making these assumptions the investigator must recall that assumptions which are true in the normal experimental animal or in patients may not be true in the presence of pathologic states or under the influence of drug therapy.

In attempts to estimate cholesterol synthesis in patients, two general approaches have been used. In the first method the patient is given a labeled precursor, such as ^{14}C-acetate, and the accumulation of labeled cholesterol in the plasma is measured. In the second method radioisotopes are not used but rather a balance study is carried out in which the dietary intake of sterol is known and the total excretion of cholesterol metabolites in the stool as bile acids and fecal sterols is accurately measured. The amount excreted in excess of dietary intake (on a mole for mole basis) represents synthesis. With the isotope method, changes in a number of factors other than cholesterol synthesis may affect the amount of radioactive cholesterol found in the plasma. These include dilution of the labeled precursor prior to its incorporation into labeled cholesterol; diversion of precursor to other metabolic pathways (such as into the synthesis of fatty acids); direct catabolism of the precursor to carbon dioxide; dilution of the labeled, newly synthesized cholesterol in the plasma by unlabeled cholesterol from other body pools (red blood cells, muscle, intestine, liver, skin, adrenals, and the nervous system); preferential movement of newly synthesized cholesterol into the plasma, the rate of cholesterol excretion as bile acids and fecal sterols, and changes in plasma volume. Changes in the rate of any of these processes would affect the percentage of the administered labeled precursor which appears in the plasma cholesterol fraction. If acetate is used as a precursor, less than 1% of the administered label appears as labeled cholesterol in the plasma. Thus it is evident that even small

Continued

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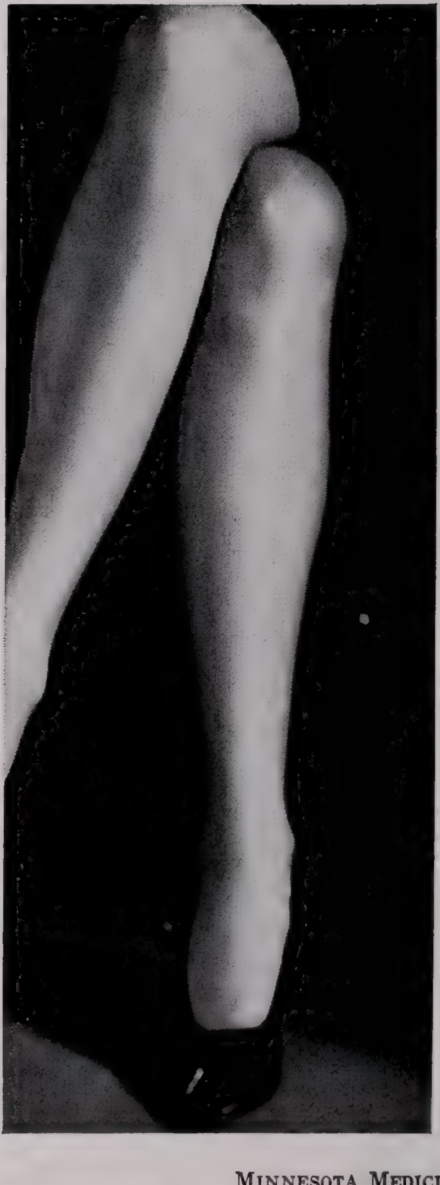

You see, a woman simply has no defense against Ultreer Elastic Stockings. They look like lovely support stockings. They feel like lovely support stockings. They're that sheer, and shapely and comfortable.

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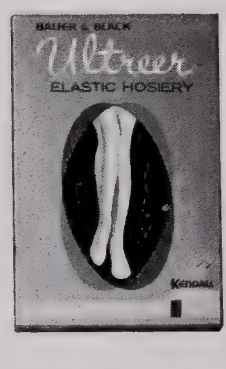
Ultreer. What a stocking.



KENDALL
BAUER & BLACK SUPPORTS DIVISION

changes in these other factors could have a profound effect.

These problems are complicated further by the fact that cholesterol is not uniformly distributed throughout the body, and the rates of exchange of cholesterol between the various body pools may vary from less than two hours, in the case of the liver, to at least a month and probably longer in the case of nervous tissue. Although information regarding the controlling factors in cholesterol synthesis is limited, available information from animal studies indicates that *liver* synthesis can be inhibited by dietary cholesterol, whereas neither *intestinal* synthesis nor *skin* synthesis is affected.[4] Recent studies [5,6] suggest that bile acids may inhibit *intestinal* cholesterol synthesis. Equilibration of intestinal cholesterol with the plasma pool is via the lymphatics, a slow system in comparison to the rapid exchange between the liver and plasma.

In their report, *Human Serum Cholesterol Synthesis,* Taylor and associates* have overcome the problem of changes in the rate of cholesterol excretion by measuring the degree of labeling of cholesterol rather than the total amount of label in the cholesterol fraction. Also, problems of dilution and preferential pool shifts of the newly synthesized cholesterol are minimized by the prolonged (40 to 50 days) period over which the precursor was given. The massive dose of the label given reduces the likelihood that diversion of the precursor to other pathways is a limiting factor. The authors' correction for the dilution of deuterocholesterol by exogenous dietary cholesterol, however, may not be valid. In their calculation, they assumed that the increase in concentrations of serum cholesterol which occurred when the subjects were changed from a cholesterol-free to a cholesterol-rich diet was merely a reflection of an increase in the size of the cholesterol pool. They did not take into account the possibilities that changes in rates of cholesterol synthesis, excretion, or distribution to other body pools may have affected the concentration of serum cholesterol. Studies by others have suggested that cholesterol synthesis by the liver is affected by cholesterol feeding.

In order to obtain the half-life of deuterocholesterol and from this to calculate its turnover and daily synthesis rate, Taylor and associates plotted their data on semilog paper after the manner of London and Rittenberg.[7] To obtain a meaningful half-life value from which a synthesis rate can be derived, this plot must be linear. While no such plot is included in this article, several are illustrated in a more detailed report of this study. These plots do not appear to be linear.[8] Therefore, while this method overcomes some of the problems, others remain.

The second method for measuring cholesterol synthesis, the balance study, also has its problems. The accurate quantitation of fecal bile acids and sterols is a difficult chemical procedure. Recently, a group at Rockefeller Institute[9,10] has overcome this problem by using a combination of thin-layer, alumina column, and gas-liquid chromatography. The other major problem of a balance study involves the possibility of a change in the total body pool of cholesterol between the study periods. Thus, the precise quantitation of cholesterol synthesis in human beings is fraught with many possible errors.

Finally, I feel that the conclusions expressed by Taylor and associates in their report need amplification. In their studies they attempted to measure *total* cholesterol synthesis in patients and were unable to demonstrate a feedback mechanism for compensating for dietary cholesterol in man. In contrast, workers proposing a feedback mechanism in rats and dogs[4,11] pointed out in their studies that this mechanism is in operation in the liver but not in the skin and intestine. Many investigators feel that the skin and intestine may be as important as the liver in total cholesterol synthesis.

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May be secured from the author or the reprints.

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Its formula consists of a combination of sodium salicylate, para-aminobenzoic acid and ascorbic acid. This special combination provides higher, longer-lasting analgesic levels compared with salicylates alone. Each P-B-SAL-C Tablet is enteric coated to delay disintegration until it reaches the small intestine.

P-B-SAL-C, low in cost to your arthritic patients, will help keep them active. Other P-B-SAL-C formulas available:
1. P-B-SAL-C with Colchicine
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3. P-B-SAL-C Sodium Free
4. P-B-SAL-C with Prednisolone (Sodium Free)

For complete information and samples, write to Dept. MM-100

FORMULA

Each enteric-coated P-B-SAL-C Tablet contains sodium salicylate 0.3 Gm., para-aminobenzoic acid 0.3 Gm., ascorbic acid 50.0 mg.

CONTRAINDICATIONS

Renal damage, salicylate sensitivity or in conjunction with sulfonamide therapy.

DOSAGE

Take 2 tablets four or more times daily.

ULMER

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Quantitative Urine Cultures*

THE CURRENT concept of enumerating microorganisms in urine as an aid in establishing a diagnosis of urinary tract infection is receiving a great deal of attention. Quantitation has merit only if careful attention is given to factors controlling the outcome of attempts to determine the number of bacteria in bladder urine.

The procedure employed in collecting a specimen for bacteriologic examination is one of the most important steps in establishing a bacteriologic diagnosis. Material to be examined bacteriologically often contains microorganisms representative of the normal or usual flora of the region. For example, sputum and feces contain many types of bacteria; and it is the responsibility of the bacteriologist to separate the usual or normal inhabitants from potential pathogens. It is virtually impossible to collect any specimen, even of blood or spinal fluid, and be absolutely assured that it will be free of an occasional contaminant. For this reason any culture procedure should provide some method of quantitating the organisms present. Unless this criterion is met, the true significance of the mere presence of organisms may not be clear.

Urine obtained by any procedure, and especially by the clean-catch method, may contain a few bacteria. Prompt transportation to the laboratory is essential, since urine may serve as a culture medium for certain bacteria. Low counts may increase to a significant level in a relatively short time; and, conversely, high counts may be reduced if there are antibacterial agents in the urine.

What constitutes a significant number of bacteria in the urine is a question for which a universally acceptable answer is still lacking. Various techniques have been described for estimating bacterial populations, none of which approach the accuracy attainable with cultures prepared by inoculating suitable media with an inoculum from a standard loop or an appropriate tube dilution of the urine.

Since obtaining urine completely free of bacteria is extremely difficult, aside from suprapubic aspiration, caution must be exercised before establishing a definitive bacteriologic diagnosis. If meticulous attention is paid to collection and transportation, if reliable quantitative bacteriologic procedures are used, and if critical evaluation of the bacterial population is made by one experienced in medical bacteriology, then quantitative urine cultures do provide clinicians with specific and accurate information.

Gerald M. Needham, Ph.D.
Rochester, Minnesota

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*Shaw, S. T., Jr., Hopp, M., and St. Geme, J. W., Jr.: Quantitative Urine Culture with a Calibrated Bacteriologic Loop: Technique Applicable to the Office Laboratory. Minnesota Med 49:749, 1966.

Hypercalcemic Crisis*

THE CLINICAL manifestations of hypercalcemia may be quite variable and may affect any body system. An awareness of the more common ones is essential to the clinician, if serious, even fatal, consequences of marked hypercalcemia are to be avoided.

Minimal hypercalcemia may be asymptomatic but is often associated with renal stones, duodenal ulcer, or pancreatitis. Higher levels of serum calcium may also be associated with these disorders, but other gastrointestinal, muscular, central nervous, and cardiovascular symptoms may predominate. Hypercalcemia should be suspected in patients with unexplained anorexia, weight loss, nausea and vomiting, severe constipa-

Continued

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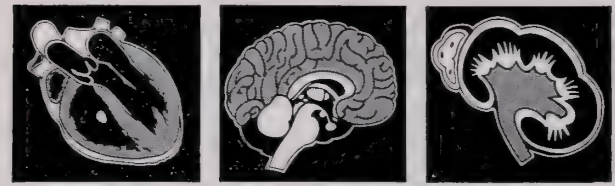
*Flink, Edmund B., Desper, Paul C. and Jones, John E.: Primary Hyperparathyroidism. Minnesota Med 49:734, 1966.

SQUIBB NOTES ON THERAPY

Behind continued high blood pressure readings lies the possibility of organic damage[1-13]

MANY OF THE aspects of essential hypertension are unpredictable—either because there are a number of mechanisms involved or because individuals differ in their responses to these mechanisms.[1]

There is one aspect of hypertension, however, that seems, in many cases, predictable. ". . . when the blood pressure is elevated to a marked degree for an adequate period of time, this in itself leads to perpetuation of the syndrome with resulting vascular damage throughout the body."[14] All too often the disease progresses until there is damage to one of three vital organs: the heart, the kidney, the brain.



> "Hypertension is certainly a major factor in the genesis of coronary heart disease, and it is even more important when compounded with obesity."[4]
>
> "[Vascular deterioration] can be clearly seen in the kidney with a degree of damage that can be measured by renal function studies."[10]

". . . most evidence suggests that reduction of blood pressure, when it is too high, not only relieves the heart of excess work but reduces vascular damage."[1]

"In short, treatment is indicated."[1]

Antihypertensive therapy will not restore the blood vessels to normal. Yet many of the vascular changes and symptoms caused by increased blood pressure may be arrested or alleviated when the blood pressure is reduced to normotensive levels.[7]

Reducing the blood pressure helps curtail further vascular damage and improves the prognosis — when damage is not too far advanced before therapy is started.[14] Essential hypertension is an indication not only for treatment, but for *early* and adequate treatment of the patient in question.

Reduce the blood pressure with Rautrax-N

Rautrax-N combines the antihypertensive-tranquilizing action of whole root rauwolfia with the antihypertensive-diuretic action of bendroflumethiazide in one convenient medication. The two drugs complement each other so that smaller doses of both are possible.

Rauwolfia combined with bendroflumethiazide is particularly effective in long-term therapy,[15-17] since beneficial effects do not diminish with continuous daily administration.

For most patients 1 or 2 Rautrax-N tablets daily are sufficient for maintenance therapy. The simplicity, convenience and economy of such a dosage schedule are of particular benefit to older patients.

References: **1.** Page, I. H., and Dustan, H. P.: The Usefulness of Drugs in the Treatment of Hypertension, in Ingelfinger, F. J.; Relman, A. S., and Finland, M.: Controversy in Internal Medicine, Philadelphia, W. B. Saunders Co., 1966, p. 95. **2.** Hollander, W.: The Evaluation of Antihypertensive Therapy of Essential Hypertension in Ingelfinger, F. J.; Relman, A. S., and Finland, M.: Controversy in Internal Medicine, Philadelphia, W. B. Saunders Co., 1966, p. 97. **3.** Nickerson, M.: Antihypertensive Agents and the Drug Therapy of Hypertension, in Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 3, New York, The Macmillan Co., 1965, p. 727. **4.** Berkson, D. M.: Indust. Med. & Surg. **32**:371, 1963. **5.** Cohen, B. M.: M. Times **91**:645, 1963. **6.** Lee, R. E., et al.: Am. J. Cardiol. **11**:738, 1963. **7.** Moyer, J. H.: Am. J. Cardiol. **9**:821, 1962. **8.** Moser, M.: New York J. Med. **62**:1177, 1962. **9.** Wood, J. E., and Battey, L. L.: Am. J. Cardiol. **9**:675, 1962. **10.** Moyer, J. H., and Heider, C.: Am. J. Cardiol. **9**:920, 1962. **11.** Moser, M., and Macaulay, A. I.: New York State J. Med. **60**:2679, 1960. **12.** Judson, W. E.: Nebraska M. J. **44**:305, 1959. **13.** Hodge, J. V.; McQueen, E. G., and Smirk, H.: Brit. M. J. **1**:5218, 1961. **14.** Moyer, J. H., and Brest, A. N.: Hypertension Recent Advances, Philadelphia, Lea & Febiger, 1961, p. 633. **15.** Berry, R. L., and Bray, H. P.: J. Am. Geriatrics Soc. **10**:516, 1962. **16.** Reid, W. J.: J. Am. Geriatrics Soc. **13**:365, 1965. **17.** Feldman, L. H.: North Carolina M. J. **23**:248, 1962.

Contraindications: Severe renal impairment or previous hypersensitivity. **Warning:** Ulcerative small bowel lesions have occurred with potassium-containing thiazide preparations or with enteric-coated potassium salts supplementally. Stop medication if abdominal pain, distension, nausea, vomiting or G.I. bleeding occur.

Precautions and Side Effects: The dose of ganglionic blocking agents, veratrum or hydralazine when used concomitantly must be reduced by at least 50% to avoid orthostatic hypotension. Caution is indicated in patients with depression, suicidal tendencies, peptic ulcer; electrolyte disturbances are possible in cirrhotic or digitalized patients. Marked hypotension during surgery is possible; consider discontinuing two weeks prior to elective surgery and observe patients closely during emergency surgery. Rauwolfia preparations may cause reversible extrapyramidal symptoms and emotional depression, diarrhea, weight gain, edema, drowsiness may occur. Bendroflumethiazide may cause increases in serum uric acid, unmask diabetes, increase glycemia and glycosuria in diabetic patients, and may cause hypochloremic alkalosis, hypokalemia; cramps, pruritus, paresthesias, rashes may occur.

Dosage and Supply: Initial dosage, 1 to 4 tablets daily, preferably at mealtime. Maintenance, 1 or 2 tablets daily. Rautrax-N is supplied as capsule-shaped tablets containing 50 mg. Rauwolfia serpentina whole root (Raudixin®), 4 mg. bendroflumethiazide (Naturetin®), 400 mg. potassium chloride.

Also available: Rautrax-N Modified — capsule-shaped tablets containing 50 mg. Rauwolfia serpentina whole root (Raudixin), 2 mg. bendroflumethiazide (Naturetin), 400 mg. potassium chloride. Both potencies available in bottles of 100. For full information, see Product Brief.

RAUTRAX®-N

Squibb Rauwolfia Serpentina Whole Root (50 mg.) with Bendroflumethiazide (4 mg.) and Potassium Chloride (400 mg.)

SQUIBB

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tion, generalized muscular weakness, altered states of awareness or consciousness, thirst, or increased urination.

Serum calcium should be determined in any patient when these symptoms cannot readily be ascribed to known associated disorders. This examination should be a part of the initial medical evaluation, since marked hypercalcemia is a medical emergency and requires prompt recognition and treatment. Death may occur during severe hypercalcemia and is usually attributed to effects on the heart.

Hypercalcemic crisis may appear in primary hyperparathyroidism, malignancy (with or without bony metastasis), vitamin D intoxication, multiple myeloma, milk-alkali syndrome, or sarcoidosis. Sufficiently elevated levels of serum calcium to reach crisis proportions could develop in many states of moderate hypercalcemia if dehydration occurs.

Hypercalcemia due to primary hyperparathyroidism is best treated by surgical exploration and removal of the abnormal parathyroid tissue, usually a single adenoma. Effective, safe, and prompt medical treatment for other hypercalcemic disorders is less satisfactory.

Correction of dehydration is of primary importance, and ancillary measures, such as the use of large doses of corticosteroids or intravenous disodium ethylene-diaminetetraacetate (EDTA), often are required. Corticosteroids have the disadvantage of a lag period that may last several days before an effective response occurs. An appreciable number of patients with hypercalcemia due to malignancy do not respond to corticosteroids with a reduction in serum calcium. Large doses of corticosteroids may be contraindicated in certain patients for other medical reasons.

EDTA infused intravenously often decreases serum-calcium levels by its chelating action, but this effect usually persists for only a short time after infusion is discontinued. Repeated administration invokes the appreciable hazard of renal damage.

Goldsmith and Ingbar[1] have used buffered phosphate solutions orally or intravenously in the management of hypercalcemia of divergent causes with good results. The potential complication of extraskeletal calcification has not been a problem in their cases. The mechanism by which reduction in serum calcium occurs is not known, but the effect is prompt; therefore this appears to be an approach to the treatment of severe hypercalcemia that merits further investigation.

Don C. Purnell, M.D.
Rochester, Minnesota

Reference

1. Goldsmith, R. S., and Ingbar, S. H.: Inorganic Phosphate Treatment of Hypercalcemia of Diverse Etiologies. New Engl J Med 274:1, 1966.

Acute Myelocytic (Granulocytic) Leukemia: Current Therapy*

VINCRISTINE AND prednisone produce a complete hematologic remission in as many as 90% of patients with acute lymphocytic leukemia, and this remission can be maintained with intermittently administered oral methotrexate for more than a year.[1] Unfortunately, treatment of acute myelocytic leukemia is much less satisfactory. In fact, 6-mercaptopurine, the current standard treatment of choice, produces a complete remission in less than 10% of patients.[2] Of all cases of acute leukemia in adults, 80% are of acute myelocytic leukemia. My colleagues and I include myelomonocytic leukemia (Naegeli) in the myelocytic leukemia group since the responses of both conditions to therapy are the same.

Because infection and hemorrhage are the two most common causes of death in acute leukemia, supportive therapy is extremely important. Fever may occur from the leukemic process itself, but in the majority of

Continued

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*Kennedy, B. J., Yarbro, J. W., and Kronenberg, R. S.: Acute Myeloid Leukemia Treatment of With 6-Mercaptopurine and Cyclophosphamide. Minnesota Med 49:1071, 1966.

when agitation

accompanies

spasm of the

'G. I.' tract.

Butadonna®

BUTABARBITAL SODIUM 15 MG. (BARBITURIC ACID DERIVATIVE)
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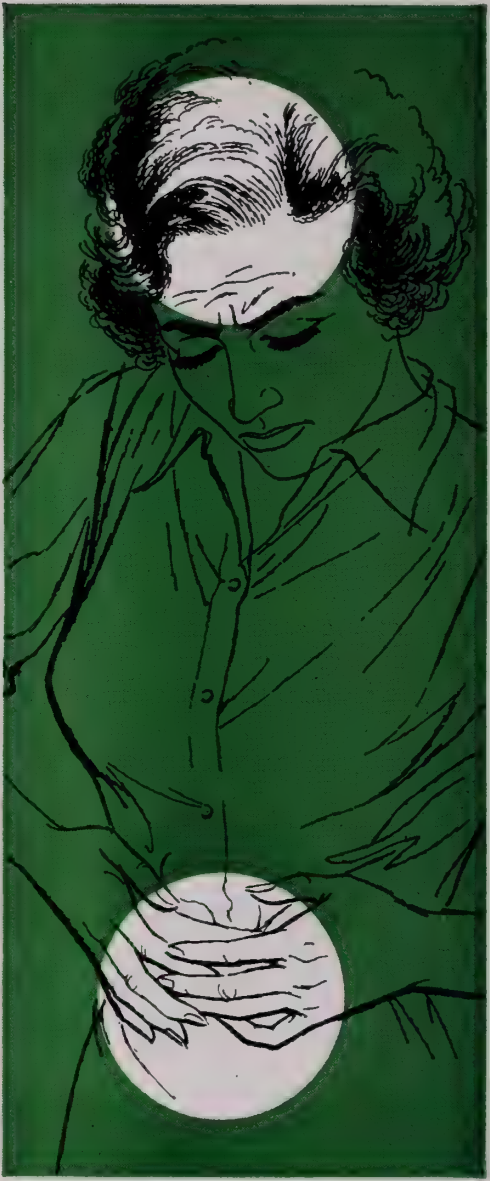
intermediate sedation and

relaxes 'G. I.' spasm.



Butadonna quiets the "brain-on-gut" influences by providing the smooth, intermediate sedative, butabarbital sodium, desirable in combination with the proven antispasmodic, belladonna extract. Butabarbital sodium is more rapidly eliminated than phenobarbital, and avoids the latter's cumulative effect.

Indications: Antispasmodic-sedative. Useful in the treatment of peptic ulcer, gastritis, duodenitis, irritable colon syndrome, ulcerative colitis, regional enteritis, and other conditions associated with gastrointestinal spasm. Also may be useful in functional dysmenorrhea.

Usual adult dosage is one tablet 3 or 4 times daily as needed.

Caution: Contraindicated in glaucoma and urinary retention. Reduce dosage or discontinue use in event of blurring of vision, dryness of mouth, tachycardia, or excessive drowsiness. Continued use of butabarbital sodium may be habit forming.

Cole

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instances it results from infection. Patients with acute leukemia are overly susceptible to infections and tolerate them poorly. Examination of the patient and cultures of blood, sputa, and urine as well as chest roentgenograms and prompt institution of appropriate antibiotics are necessary. My colleagues and I do not believe that the use of prophylactic antibiotics is indicated in these cases. If available, granulocyte transfusions may be helpful for the patient with neutropenia. Infusion of fresh blood or platelet-rich plasma may be lifesaving in the event of severe bleeding from thrombocytopenia.

Oral ulceration may prove very troublesome and can be alleviated with the use of viscous xylocaine before meals. A protective-emollient preparation (Orabase) can be used to cover an ulcerated lesion. Mouthwashes with hydrogen peroxide also decrease local oral discomfort. Nystatin (Mycostatin) or gentian violet is usually very beneficial in the treatment of oral moniliasis.

Radiation is generally contraindicated in acute leukemia, but very small doses have been helpful in instances of localized bone pain, ulceration, or chloroma.*

Since orally-administered 6-mercaptopurine is ineffective for the majority of patients with acute myelocytic leukemia, much effort has been made to devise new therapy. The combination of 6-mercaptopurine and cyclophosphamide as described in this issue produced a constant decrease in leukocytes and myeloblasts; but bone-marrow remissions were documented in only two cases. This particular mode of therapy cannot be recommended at present. However, the increase in hemoglobin concentration and platelet count is of interest, and future studies with these therapeutic agents may be fruitful.

The use of corticosteroids in acute myelocytic leukemia is controversial. Despite other opinions, my colleagues and I consider that prednisone is not contraindicated and that, after 6-mercaptopurine failure or in the event of significant bleeding, an initial dose of 100 to 150 mg. of prednisone daily can be given, along with antacids and a bland diet in order to decrease the possibility of peptic ulceration.

We have used methylglyoxyl-bis-guanylhydrazone dihydrochloride (methyl-GAG), an investigational drug effective against L 1210 mouse leukemia, in human beings. Despite earlier optimistic reports, our recent studies record a rate of remission of no more than 25%. Intravenous administration of the drug produces considerable gastrointestinal toxicity, but intramuscular injections are less toxic. In our experience, methyl-GAG and hydroxystilbamidine have not been helpful despite initial encouraging experience in animals. Methyl-GAG combined with 6-mercaptopurine was reported to have resulted in remission in one third of 42 patients with acute myeloblastic leukemia.[3]

A combination of vincristine, methotrexate, 6-mercaptopurine, and prednisone in large doses has been used, with some increase in remission rate, but unfortunately, this large dose schedule is very toxic. Recently, Thompson and associates[4] have reported encouraging results, after utilizing smaller doses of these four drugs. Further studies are needed.

Cytosine arabinoside, given intravenously, has produced complete bone-marrow remission in 12 of 77 patients with acute myelocytic leukemia.[5] This drug requires further evaluation.

Treatment of acute myelocytic leukemia has been discouraging. The chemotherapeutic agent of choice at present remains 6-mercaptopurine. In all cases, supportive treatment at the same time is usually necessary.

Robert A. Kyle, M.D.
Rochester, Minnesota

See Test Your Word Score Page 1719.

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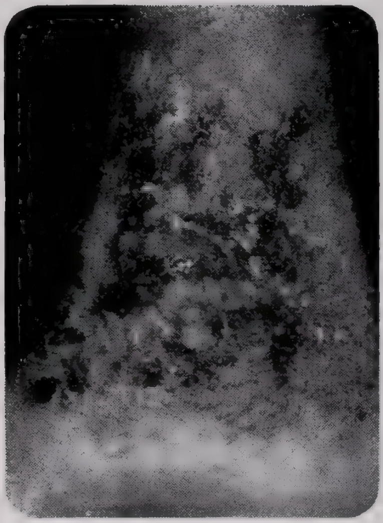
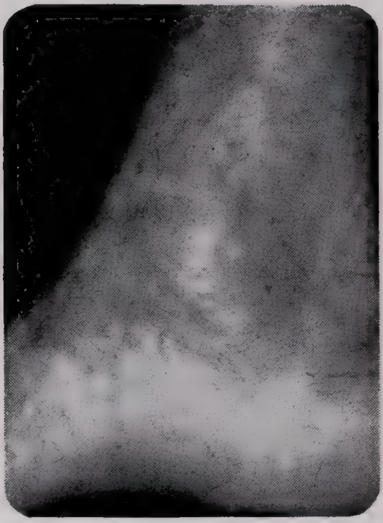
3-5 May be secured from the author or the reprints.

eczema: scourge of childhood



R. R., Age 11 — Before treatment — atopic eczema of long standing



After treatment — with ARISTOCORT Topical Ointment 0.1% for two weeks

ARISTOCORT® Triamcinolone Acetonide Topicals have proved exceptionally effective in the control of various forms of childhood eczema: allergic, atopic, nummular, psoriatic, and mycotic.

In most cases responsive to topical ARISTOCORT, the 0.1% concentration is sufficiently potent. The 0.5% concentration provides enhanced topical activity for patients requiring additional potency for proper relief.

Administration and Dosage: Apply sparingly to the affected area 3 or 4 times daily. Some cases of psoriasis may be more effectively treated if the 0.1% Cream or Ointment is applied under an occlusive dressing.

Contraindications: Tuberculosis of the skin, herpes simplex, chicken pox and vaccinia.

Precautions and Side Effects: Do not use in the eyes or in the ear (if drum is perforated). A few individuals react unfavorably under certain conditions. If side effects are encountered, the drug should be discontinued and appropriate measures taken. Use on infected areas should be attended with caution and observation, bearing in mind the potential spreading of infection and the advisability of discontinuing therapy and/or initiating antibacterial measures. Generalized dermatological conditions may require systemic corticosteroid therapy. Steroid therapy, although responsible for remissions of dermatoses, especially of allergic origin cannot be expected to prevent recurrence. The use over extensive body areas, with or without occlusive nonpermeable dressings, may result in systemic absorption. Appropriate precautions should be taken. When occlusive nonpermeable dressings are used, miliaria, folliculitis and pyodermas will sometimes develop. Localized atrophy and striae have been reported with the use of steroids by the occlusive technique. When occlusive nonpermeable dressings are used, the physician should be aware of the hazards of suffocation and flammability. The safety of use on pregnant patients has not been firmly established. Thus, do not use in large amounts or for long periods of time on pregnant patients.

Packages: Tubes of 5 Gm. and 15 Gm.; ½ lb. jar.

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Aristocort® Topical Ointment 0.1% and Cream 0.1%, 0.5%
Triamcinolone Acetonide
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618-

Surgery for the Carotid Artery

THE FINE ARTICLE by Garamella et al. published in this issue of Minnesota Medicine* attests to their technical proficiency in restoring flow in occluded carotid arteries. It is good also that the medical profession be exposed to a positive approach in this very common problem. However, in all fairness to our medical audience, it should be stressed that restoration of flow in totally occluded carotid arteries is not synonymous with restoration of function and, in fact, may cause a worsening of the patient's condition by way of hemorrhage to an area of ischemic brain.

Dr. Garamella mentions the vagaries of interpreting his data. The results in his patients wherein flow was successfully reestablished are better, but not markedly so, than in the patients where flow was not reestablished.

At the present time the best results are obtained when surgery is performed on those patients with intermittent symptoms who have had careful study of the carotid and vertebral system and in whom a partially occluded vessel is demonstrated. The question of whether surgery should be advised for the completed stroke patient remains a moot one. Hopefully, a carefully randomized study will, in the future, clarify the issue.

Harrison H. Farley, M.D.
Minneapolis, Minnesota

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*See page 1669.

Importance of National Program for Aerospace Medicine

GENERAL NIESS* has pointed out lucidly the need for continued support of our national aerospace research program. Many persons are confused as to the purposes of the national program of research in aerospace medicine and have difficulty in understanding the purposes behind such a program. In particular, it is very difficult for the uninformed to understand how anything "practical" can be derived from space research. I think General Niess has clarified this question very well indeed.

General Niess also has set forth the prevailing philosophy of those engaged in aerospace medical research, and I am sure he has explained some of the thinking behind the work of a large number of biologists and other aeromedical scientists busily engaged in this very broad field of research.

Earl T. Carter, M.D., Ph.D.
Rochester, Minnesota

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*Niess, O. K.: Space Laboratories for Research in Biology and Medicine: Promising Developments. Minnesota Medicine 49:1323, 1966.

Test Your Word Score

Fortuitous — *happening by chance or accident* (page 1701).
Cybernated — *controlled by cybernetics: the science of control and communication processes in animals and machines, dealing with information processing systems by means of computers* (page 1705).
Chloroma — *a condition characterized by periosteal tumor-like growths and by a blood picture resembling leukemia* (page 1717).
Incudomalleal — *pertaining to the incus and malleus* (page 1743).
Lamina cribrosa — *a horizontal plate from which are suspended the lateral mass and the lamina perpendicularis* (page 1744).
Hyponatremia — *deficiency of sodium in the blood* (page 1749).
Natruresis — *excretion of sodium ions in the urine* (page 1751).
Mannitol — *an unfermentable hexahydroxy alcohol, used to measure the rate of glomerular filtration* (page 1751).

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You May Be Right

Utilization of Thebesian Blood Flow in Treatment of Coronary Heart Disease

The heart musculature has a double blood supply. Seventy-eight percent of the blood supplying the heart muscle comes from the coronary artery, and 12 percent comes through by way of the thebesian vein.[1]

Prinzmetal[2] placed microscopic beads in the auricle and traced them into the coronary circulation.

Vineberg[3] and Lillehei[4] have demonstrated that they can save victims of coronary heart disease by inserting a bleeding artery or vein directly into the damaged musculature of the heart, thus giving the heart the opportunity to survive. Nature has supplied us at birth with these passages to deliver blood and oxygen to distressed heart muscles when in need. Several authors[5,6,7] have stated that the heart can be so trained by gradual adaptation to stress, if one can learn how to utilize the function of the thebesian venous system, thus providing a blood supply to the heart musculature by an ebb and flow process. Then it may be possible to prevent or delay complete heart failure.

The surgical method of providing blood to the heart by suturing a bleeding vessel into a prepared groove becomes possible because the heart muscle is sponge-like in its structure. Hence the reaction is similar to pouring into a sponge fluid which quickly disperses throughout, so that as the sponge is squeezed more fluid can be absorbed. Is it not possible that this is precisely what happens in systole and diastole when the spongy heart muscle[8] receives the blood from the thebesian vein and into the loose musculature of the ventricle, producing, in effect, a profusion of blood to nourish the injured ventricular muscular?

My first experience was obtained from the history of a man[8] who suffered from angina and, unable to find his nitroglycerine, gasped with delight as he heard the beautiful singing of a bird. As he did this his angina disappeared, and from that I developed the process of controlled deep breathing as a method of endeavoring to produce an ebb and flow type of blood perfusion through the thebesian vein.

By a process of controlled diaphragmatic breathing, every five minutes out of every two hours the patient is taught to utilize the ebb and flow of the arterial and venous blood to aid in perfusing the heart musculature.

By this method I have observed beneficial results in more than one hundred patients whom I have treated .

*See page 1669.

Aaron Friedell, M.D.
Minneapolis, Minnesota

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2-8. May be secured from the author.

The alienist is not a joke; He finds you cracked, and leaves you broke. —
Keith Preston

Most of my patients with high blood pressure are as old as I am. A lot of them are living on pensions. They're grateful when I can keep prescription costs down.

Regroton®

chlorthalidone 50 mg. reserpine 0.25 mg.

1 tablet daily brings pressure down

Advantage: Both components of Regroton are long-acting.
Average dosage: One tablet daily with breakfast.
Contraindications: History of mental depression, hypersensitivity, and most cases of severe renal or hepatic diseases.
Warning: Discontinue 2 weeks before general anesthesia, 1 week before electroshock therapy, and if depression or peptic ulcer occurs. With administration of enteric-coated potassium supplements, the possibility of small bowel lesions should be kept in mind.
Precautions: Reduce dosage of concomitant antihypertensive agents by one-half. Discontinue if the BUN rises or liver dysfunction is aggravated. Electrolyte imbalance and potassium depletion may occur; take particular care in cirrhosis or severe ischemic heart disease, and in patients receiving corticosteroids, ACTH, or digitalis. Salt restriction is not recommended. Use with caution in patients with ulcerative colitis, gallstones, or bronchial asthma.
Side effects: Nausea, vomiting, diarrhea, muscle cramps, headaches and dizziness. Potential side effects include angina pectoris, anxiety, depression, drowsiness, hyperglycemia, hyperuricemia, lassitude, leukopenia, nasal stuffiness, nightmare, purpura, urticaria, and weakness.
For full details, see the complete prescribing information.
Availability: Bottles of 100 and 1000 tablets.

Geigy

Curbstone Consultation

Jaundice and Kernicterus

QUESTION: In which cases of jaundice in infants is kernicterus most likely to be damaging?

ANSWER: Jaundice is most likely to be damaging if a. jaundice is due to hemolytic disease of the newborn; b. the infant is premature, especially of less than 5 lbs; c. jaundice is associated with anoxia, free fatty acids in the serum (as in starvation), or sulfa drugs; d. jaundice is associated with low serum albumin.

There are varying degrees of kernicterus and follow-up in most studies is inadequate. For a good discussion of the problems surrounding "physiologic jaundice" in both premature and full-term infants see R. L. Day, Pediat Clin N Amer 8:539, 1961.

I believe the answer in the toxicity of indirect bilirubin in newborns is whether the infant has enough serum albumin to bind all its indirect bilirubin. We now have a simple lab test available to measure the serum albumin which is free to combine with additional indirect bilirubin and keep the bilirubin from going into the cells.*

The physician who knows both the indirect bilirubin level and the albumin-binding capacity should be able to prevent all cases of kernicterus without subjecting to exchange transfusion infants who don't really need it.

Virginia Y. Blacklidge, M.D.
University of California
Berkeley, California

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*Waters, W. J., and Porter, E.: Indications for Exchange Transfusion Based upon the Role of Albumin in the Treatment of Hemolytic Disease of the Newborn. Pediatrics 33:749, 1964.

Vaginal Discharge

QUESTION: Does the wearing of high heels affect vaginal discharge?

ANSWER: Vaginal discharge is a common gynecological symptom. Patients may claim that discharge is related to special situations. There is no evidence to indicate that the wearing of high heels or any other kind of heel would or could actually cause or increase vaginal discharge. On the other hand, violent activity or jarring of the body may be associated with the escape of vaginal moisture. Normal moisture is present in all women. Sports like tennis, horseback riding, and walking with high heels may cause the material to descend to the introitus. One should inspect carefully the cervix of these patients. A cervicitis or excessive cervical secretion may be present. Douches and vaginal inserts are without value in correction of cervicitis or excessive cervical secretion.

H. Close Hesseltine, M.D.
Dept. of Obstet. & Gynec.
University of Chicago

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The Viewing Box

Lesions of the Pelvis

in a

59-Year-Old Woman

A 59-year-old woman complained of easy fatigability and back distress since a hysterectomy in 1956. The operation was followed by roentgen therapy to the pelvis. Five months prior to this 1966 study she developed left leg weakness and a mild left pelvic pain radiating to the thigh. This was relieved by Bufferin.

The x-ray (Figure 1) reveals a generalized extensive coarsening of the trabecular pattern and loss of normal mineralization interspersed with practically intact bone above the acetabular fossae bilaterally. There is an area over the superior aspect of the left iliac bone measuring 10 cm. in greatest diameter which reveals extensive dense mineralization and fairly sharp delineation. Throughout the pelvis no frank destruction is seen and there is no evidence of old or recent fracture.

What is your diagnosis? (See next page.)

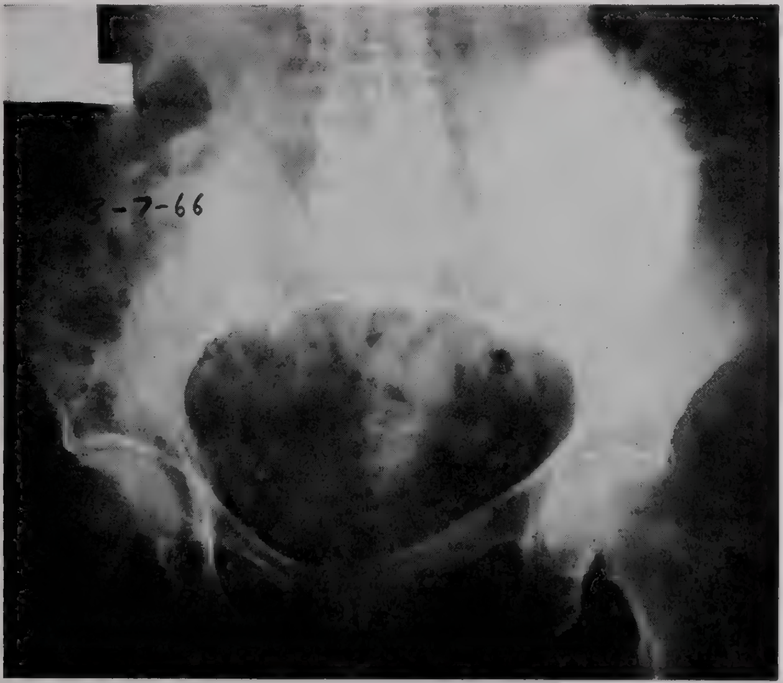

Figure 1

DIAGNOSIS: **Post Radiation Osteogenic Sarcoma**

The vulnerability of bone and cartilage to the effects of radiation are well known and were observed shortly after radiation was first utilized. Exclusive of multiple myeloma, osteogenic sarcoma is the most commonly encountered malignant primary bone tumor and also appears to be the most common of the radiation-induced sarcomas.[14]

Of almost 6,000 patients reported by Phillips and Sheline,[11] sarcomas developed in only two, giving an incidence of 0.3%, or 0.1% of the 2,300 five-year cancer survivals. Thus, although radiation induction of bone sarcoma does occur in normal bone, it is a rare complication of radiation therapy for malignant disease. The present case, for example, is the fourth reported case following external beam therapy for cancer of the cervix.[1,11,15]

The first convincing reports indicating that irradiation of bone may be followed by the development of sarcoma refer to those patients who were irradiated for tuberculous joints or chronic osteomyelitis.[15] Others[5,13] have emphasized this sequence after radiation therapy for benign bone tumors. The most spectacular example of bone sarcoma resulting from radiation has been found in dial painters who repeatedly ingested minute amounts of radium, mesothelium or radiothorium. Hatcher[8] also showed that radiation could cause sarcomas in healthy bone and that these may occur following treatment for dermatoses or malignancy.[13]

The ages of patients at the time of appearance of these iatrogenic sarcomas which have developed in normal bone or a benign bone lesion range from 4-68 years, averaging 37 years.[15] Spontaneous osteogenic sarcomas, however, develop in a younger age group insomuch as almost half occur from 10-19 years.[6]

The time from the last radiation to the onset of clinically determinable sarcomatous change is defined as the latent period.[4,6] It has ranged from 4-30 years, averaging 12, 8.6, 20 and 13.5 years in recent large series.[4,10,13,15]

The most prominent symptoms of malignant change are the rather sudden onset of constant and progressive pain and tenderness and the presence of a local mass.[12]

In general, patients have received rather large doses of low energy radiation; a threshold dose of 3,000 r. with repeated exposure has been reported.[10] However, secondary malignant bone tumors may develop after small doses in children.[5] Moreover, it has been established[7] that in most cases there is a factor of skin change and radiation damage to adjacent structures. Gonadal dysfunction, soft tissue damage, disturbed bone growth, radiation osteitis, avascular necrosis, sequestration and pathological fractures have been associated with this condition.[13]

Cahan et al.[4] defined the prerequisites of the condition (satisfied in this case):

1. There must have been microscopic or x-ray evidence of the nonmalignant nature of the initial bone condition.
2. Irradiation must have been given and the sarcoma that subsequently developed must have arisen in the area included within the radiotherapeutic beam.
3. A relatively long asymptomatic latent period must have elapsed

after irradiation before the clinical appearance of the bone sarcoma.

4. All sarcomas must have been proven histologically.

During the latent period changes occur which can be described as precancerous: they are progressive, almost always resulting in fibrosis, scarring and atrophy. The osteitis has been attributed to the finding that osteoblasts are more sensitive to irradiation than osteoclasts. Hence osteoporosis may be the result of a disturbance in the normal balance between resorption and production of bone.[9] Cruz et al.,[7] in noting the associated radiation osteitis of an extreme degree, have suggested that sarcomatous change occurs in bone which has suffered an intermediate damage. Raventos[12] feels, however, that the present evidence does not permit any conclusion as to whether the radiation-induced sarcoma most often arises in bone which has undergone radiation resorption or in areas of lesser damaged bones. Hatcher[8] suggested that bone rich in hematopoietic tissue or reticuloendothelial cells might be more prone to develop sarcoma than bones which have a greater proportion of fatty marrow. It has also been suggested that the predisposition of the individual to neoplastic growth is a factor in development of radiation sarcoma.

Though Cruz[7] reported two cases remaining free of disease following amputation, it is the experience of Steiner[15] that once a sarcoma has appeared in irradiated bone the possibility of survival is minimal even if the affected part is amputated promptly.

Radiation nephritis, pneumonitis, myelitis can be almost completely guarded against and iatrogenic carcinogenesis can be greatly reduced.[2] However, some sarcomas following irradiation will continue to occur. It is hoped that with greater utilization of supervoltage and less bone absorption of energy per roentgen the incidence of bone sarcoma will be reduced just as there has been a reduction of mandibular necrosis and

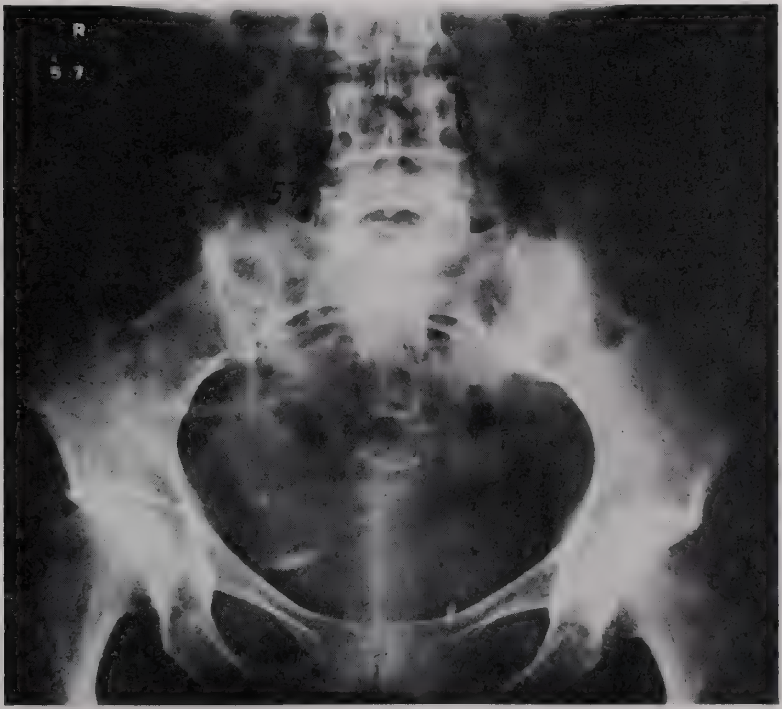

Figure 2

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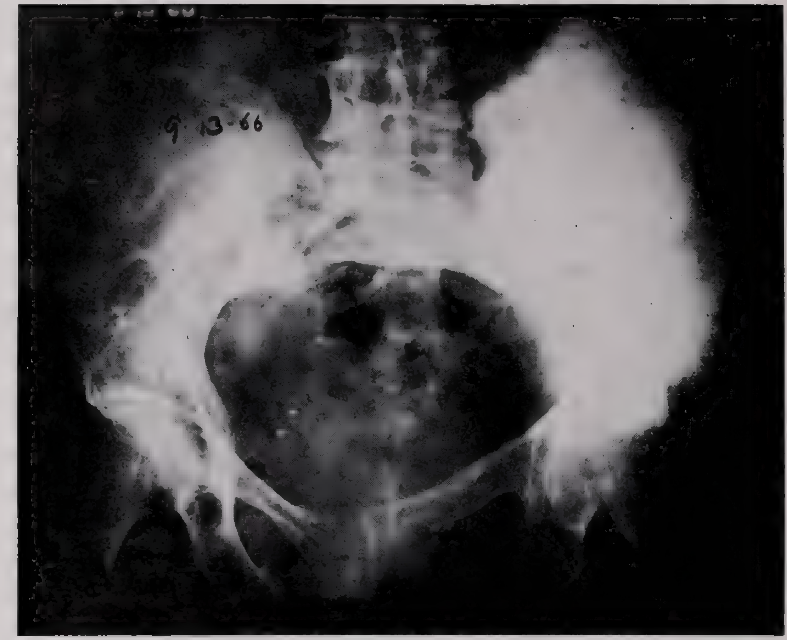

Figure 3

chondronecrosis of the laryngeal cartilage.[2]

It has been recommended[2,3,11] that benign lesions treatable by other means should not be treated with irradiation and that radiotherapy in children should be limited to the treatment of carcinoma.

In the case discussed the tumor arose in normal bone (Figure 2) which had been in the field of irradiation. Following a panhysterectomy in 1956, histological studies revealed an infiltrating anaplastic carcinoma of the cervix. Roentgen therapy was administered with the following technical factors: 200 kvp; thoraeus filter; 20 ma.; 50 cm. tsd. A daily exposure of 350 r. in air was given to one of five fields (anterior, right and left posterior, and right and left lateral). The fields, which measured 10 × 15 cm., extended from the iliac crest to the pubic level. Thirty treatments were given with a total exposure dose of 2,100 r. in air to each field in 33 days. Subsequently, the patient developed an acute dermal reaction which was followed by severe scarring and telangiectasia.

The radiograph (Figure 1, previous page) has demonstrated a generalized radiation osteitis and an osteogenic sarcoma of the left iliac bone, confirmed by biopsy 2/28/66. Note the progressive increase in the size of the lesion six months later (Figure 3), at which time she was referred for palliative radiotherapy.

Donald E. Dietrich, M.D.*
Duluth, Minnesota

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*Department of Radiology, The Duluth Clinic, LTD.

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4-15 May be secured from the author or the reprints.

Psychologist: a man who, when a beautiful girl enters the room, watches everybody else. — Bruce Patterson

Clinical Path Conference

Aortic Insufficiency and Bacterial Endocarditis

Dr. Francis J. Everhart:*

A 56-year-old mother of three was admitted to the hospital on June 22, 1966, because of bacterial endocarditis which had been recently diagnosed in her home community. A cardiac murmur was first discovered in 1950, but there was no history of rheumatic fever. After an episode of acute pulmonary edema in September, 1959, administration of digitalis and diuretics was begun and, with a few lapses, had been continued to the time of this, the final admission.

Nine days before the last admission the patient developed an upper respiratory infection and had chills, fever and a mild sore throat. Tetracycline of an unknown dosage was given orally for three days, ending June 15. Four days later, on June 19, there was recurrence of fever and chills, as well as malaise and headache. At this time the patient was hospitalized in her home community, at which time the blood pressure was 170 mm. Hg. systolic and 66 mm. Hg. diastolic. The pulse rate was 80 beats per minute and the body temperature was 104° F. Neither the spleen nor the liver was enlarged, and there were no petechiae. Blood cultures were done on June 19 and 20; both showed beta hemolytic streptococci. One gram of a tetracycline had been given intravenously on June 20. The patient was transferred on June 22, 1966.

Significant events in the medical history included several illnesses. A carcinoma of the colon had been resected in 1951, and there was no evidence of recurrence. A self-limited episode of pneumonia occurred in April, 1959. In 1964, partial loss of vision had been caused by occlusion of the left central retinal artery, and an anticoagulant (sodium warfarin) was administered. Subsequently the vision returned to normal, and treatment with anticoagulants was continued until the time of the final admission. There was a history of sensitivity to penicillin, and a few days

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before this admission a severe rash had occurred after a test injection of penicillin intradermally. The patient had taken guanethidine for hypertension for some years.

Physical examination at the time of admission showed a moderately ill patient without peripheral cyanosis or edema. A few splinter hemorrhages were present under the toenails and fingernails. The blood pressure was 156 mm. Hg. systolic and 62 mm. Hg. diastolic. The pulses were regular and the rate was 100 beats per minute. The peripheral pulses were of a "collapsing" type, considered typical for aortic insufficiency. Pulsus alternans was noted by one experienced observer. A left parasternal heave was present, and the point of maximum cardiac impulse was in the left midclavicular line at about the sixth intercostal space. The first cardiac sound was normal and the second sound was single. A grade 3/6 systolic ejection-type murmur was present over the "aortic area" and radiated to the neck. Also, a grade 3/6 holodiastolic blowing murmur was heard along the left sternal border. Over the cardiac apex a prominent third sound and a diastolic rumble of the Austin Flint variety were present. The liver was not enlarged, but there may have been a small degree of splenic enlargement.

Ophthalmoscopic examination showed slight narrowing of the left retinal artery and arteriovenous nicking bilaterally. No retinal hemorrhages were seen.

Laboratory studies, done shortly after admission, gave the following results. The hemoglobin concentration was 14.3 grams per 100 ml. of blood. The total leukocyte count was 14,150 cells per cu. mm. The differential leukocyte count was: neutrophils, 79 per cent; lymphocytes, 12 per cent; and monocytes, 9 per cent. No phagocytic histiocytes were found. The hematocrit was 37 per cent and the reticulocytes numbered 1.1 per 100 erythrocytes. The platelet count was 200,000 per cu. mm. The erythrocyte-sedimentation rate was 107 mm. per hour. Subsequently, the sedimentation rate exceeded 100 mm. per hour several times.

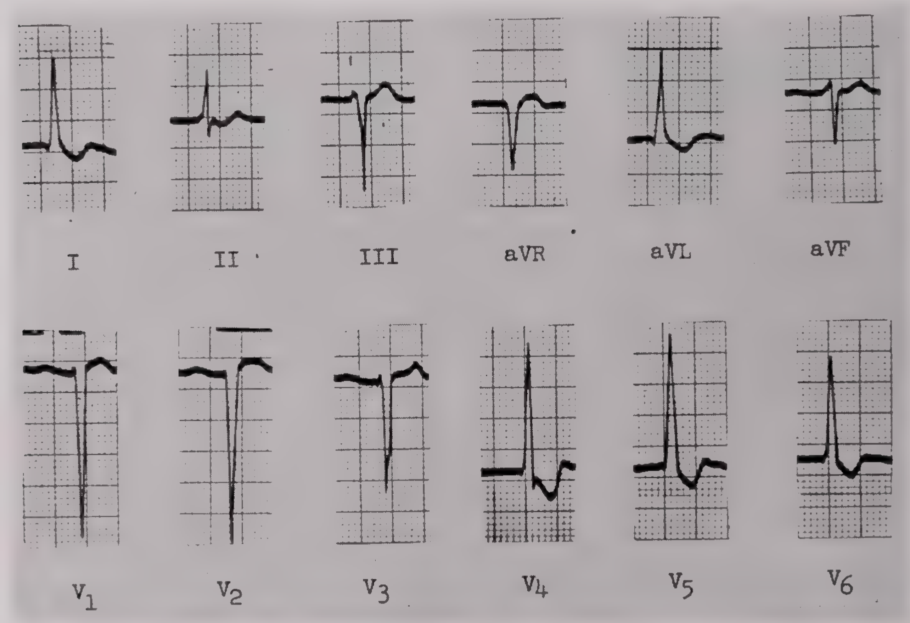

Fig. 1 — Electrocardiogram taken at the time of final admission.

Chemical determinations gave the following results: urea nitrogen, 24 (later study, 10); two-hour postprandial glucose, 64; the direct fraction of bilirubin, 0.2, and the total, 0.7; each in milligrams per 100 ml. of blood. The value for alkaline phosphatase was 9 Bodansky units. The concentration of albumin and globulin in the serum was 3.2 grams per 100 ml. and 3.8 grams per 100 ml., respectively. The VDRL test for syphilis was negative. Levels of serum lactic dehydrogenases were within the upper range of normal. The first test, which was done on the twenty-third hospital day, showed a value of 164 units for the heat stable fraction and 724 units for the total value. A second test, which was done four days later, showed values of 107 and 432, respectively. A third test showed no significant change. The concentration of creatinine was 1.1 mg. per 100 ml. of serum. The creatinine clearance tests gave normal values of 92 and 98 liters per 24 hours. The urine contained a trace of protein but was otherwise normal.

The first electrocardiogram showed left ventricular hypertrophy and strain (Figure 1).

With fluoroscopic examination of the thorax, calcification in the area of the aortic valve and left ventricular hypertrophy were observed. Wide systolic pulsations of the entire thoracic aorta were readily apparent. With barium in the esophagus, roentgenograms confirmed the presence of left ventricular hypertrophy (Figure 2).

Some of the pertinent clinical features are shown in Figure 3. This shows the highest temperature and the dosage of antibiotics, as well as the variations in hemoglobin concentrations and total leukocyte counts. Initially, antibiotics were not administered until blood cultures had been done several times. On the second hospital day the temperature rose to 104.6° F. and the patient had a shaking chill. At this time administration of antibiotics was begun with the following schedule: 3.0 grams of cephalothin, intravenously, every six hours, and 0.5 grams of streptomycin, intramuscularly, every 12 hours. Two blood cultures, which had been transferred with the patient, revealed beta streptococci, which were later found to be Group B beta hemolytic streptococci.

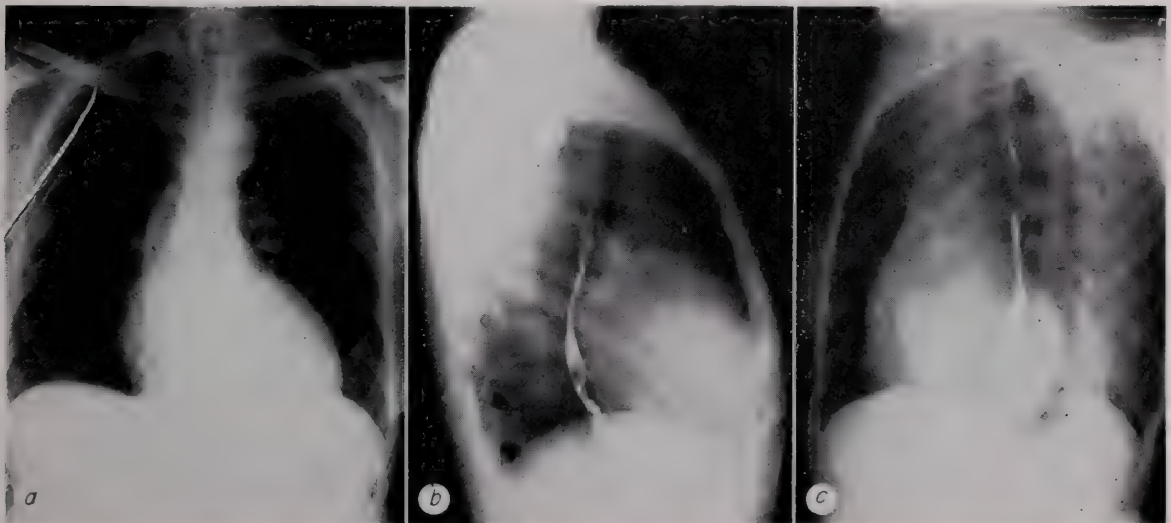

Fig. 2 — Roentgenograms of thorax. *(a)* frontal, *(b)* lateral, and (c) left anterior oblique views, respectively.

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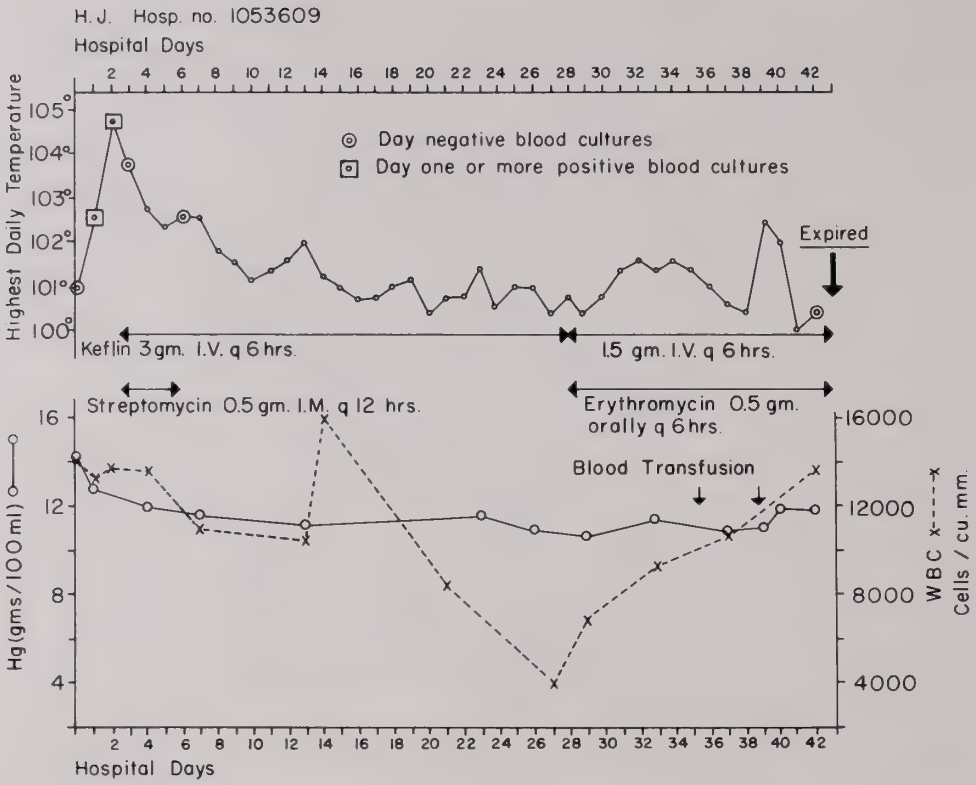

Fig. 3 — Summary of antibiotic treatment, results of blood cultures, and related response.

The organism's susceptibility to streptomycin, tetracycline, erythromycin and cephalothin is given in Table 1. Additional studies were done on a culture which was positive on the second hospital day, and this organism's susceptibility to penicillin, chloramphenicol, kanamycin, and lincomycin is also given in Table 1. The initial four cultures of the blood were sterile, whereas the succeeding six blood cultures, which were done during the first and second hospital days, were positive for Group B beta hemolytic streptococci. The colony count ranged from seven to 20 colonies per ml. of blood. After administration of antibiotics the blood remained sterile. The temperature fell somewhat, but remained above normal until the patient died. Administration of digitalis was stopped at the time of admission because sensitivity to this drug was suspected. After administration of digitalis was restarted on the tenth hospital day, it was necessary frequently to change the dosage because of rhythm disturbances. Beginning on the twenty-eighth hospital day, the patient had attacks of thoracic pain which appeared to be angina. The pain, which often occurred at night, was relieved by nitroglycerin. During this time the murmur of aortic insufficiency became more prominent. The hemoglobin concentration fell slowly and two blood transfusions were given. The second was followed by elevation of the body temperature to 102.4° F. During the evening of the forty-second hospital day the patient had an attack of severe thoracic pain which persisted for about one-half hour, despite the fact that three tablets of nitroglycerin were taken. The patient died several hours later.

Dr. James N. Karnegis will discuss the differential diagnosis.

TABLE I

Sensitivity to Antibiotics of Beta Hemolytic Streptococcus Recovered from Blood

Sensitive to	Resistant to
Streptomycin (50*)	Streptomycin (25*)
Tetracycline (1.5*)	Tetracycline (0.8*)
Erythromycin (Less than 0.4*)	
Cephalothin (Less than 0.4*)	
Penicillin (0.2 units/L.)	Penicillin (0.1 unit/L.)
Chloramphenicol (12.5*)	Chloramphenicol (6.3*)
Kanamycin (100*)	Kanamycin (50*)
Lincomycin (1.5*)	Lincomycin (0.8*)

*Micrograms per liter.

Dr. James N. Karnegis:**

The history and physical examination indicate cardiovascular disease. The fact that the patient had been treated for carcinoma of the colon does not appear to be a factor in the final illness.

The acute nature of the illness is illustrated by the fact that only about seven weeks elapsed from the time the patient first developed symptoms to her death. It seems obvious that the major disease was severe infection. The referral diagnosis was bacterial endocarditis. The fever, chills, malaise and headache were consistent with that condition, and the diagnosis was made by the isolation of beta hemolytic streptococcus from the blood. No reference is made in the initial physical examination to the presence of a cardiac murmur, but the wide systemic arterial pulse pressure would be consistent with aortic reflux.

More physical findings of bacterial endocarditis were evident upon admission to the second hospital. Subungual splinter hemorrhages were noted. The statement about a suggestion of mild splenomegaly being present is of no value. However, clear-cut cardiac findings were described. A wide systemic arterial pulse pressure was again recorded together with the collapsing pulse of aortic insufficiency. This was further confirmed by auscultation of an aortic diastolic murmur. The aortic systolic murmur, while suggesting aortic stenosis, could also be caused by the increased stroke volume resulting from aortic insufficiency alone. The single second cardiac sound could represent stenosis of the aortic valve with resultant absence of an aortic valvular closure sound, or pulmonary hypertension with the pulmonic valve closing earlier than normal in the cardiac cycle, superimposing the pulmonic on the aortic component of the second sound. Pulmonary hypertension could have been caused by congestive heart failure, but we cannot be sure of this since no mention is made of examination of the lungs. Pulsus alternans generally is taken to indicate left ventricular decompensation, and the third heart sound is consistent with that. It is more likely, however, that the single second sound resulted from aortic valvular stenosis, since the elevation of pulmonary pressure in this case would not be expected to be of sufficient magnitude altogether to prevent respiratory splitting of the second cardiac sound. A left parasternal heave indicates right ventricular hypertrophy, but since there is no other evidence for right ventricular hypertrophy we cannot be certain that such a heave was

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actually present. A diastolic rumble was interpreted by the observers to be of the type heard in patients who have aortic insufficiency but not mitral stenosis. This murmur is believed to be caused by the aortic regurgitant jet of blood striking the anterior leaflet of the mitral valve and deflecting it into the pathway of blood being expelled in diastole from the left atrium into the left ventricle. The Austin Flint murmur mimics that of mitral stenosis but can be distinguished by other auscultatory findings. In mitral stenosis one would expect an accentuated rather than a normal first cardiac sound, and an opening snap rather than a third sound.

Laboratory studies showed mild leukocytosis and a neutrophilia. Renal and hepatic tests were normal. The erythrocyte-sedimentation rate is of diagnostic importance, being virtually always elevated in bacterial endocarditis, and was quite high in this case. The electrocardiogram showed a normal electrical axis in the frontal plane, left ventricular hypertrophy and digitalis effect. The normal sinus rhythm and absence of p mitrale provide some additional evidence to help exclude mitral stenosis.

Thoracic roentgenoscopy further defined aortic insufficiency by demonstrating marked pulsation of the thoracic aorta and left ventricular hypertrophy. Although the barium-filled esophagus is somewhat displaced in the region of the left atrium, it is probable that this is caused by left ventricular hypertrophy rather than pathological enlargement of the left atrium from mitral stenosis. Calcification was definitely seen in the aortic valve but not in the area of the mitral valve. Aortic valvular calcification is of key importance in this case and indicates calcific aortic stenosis.

Calcific aortic stenosis may be complicated by embolism, and this could explain some of the previous illnesses mentioned in the history. The occlusion of the left central retinal artery may have been embolic, and the systemic hypertension could have been produced by renal embolism. Since there is no definite evidence of mitral stenosis, the etiology of the aortic stenosis could well have been congenital rather than rheumatic. One would then expect a bicuspid or perhaps unicommissural aortic valve. A bicuspid aortic valve, whether congenital or acquired, is known to be fertile ground for the development of bacterial endocarditis. The aortic insufficiency displayed by this patient could have been related to the calcific stenosis with deformity and immobilization of the leaflets, thus resulting in incompetence. The aortic insufficiency could also have been caused by the endocarditis destroying valvular tissue with perforation or prolapse of the leaflets, or by vegetations interfering with coaption and closure of the leaflets.

Beta hemolytic streptococcus is a microorganism which often causes acute bacterial endocarditis. It is a virulent organism, and thorough treatment should be started immediately. Even when the infection has been eradicated the patient may still succumb, for example, to uncontrollable heart failure resulting from the valvular insufficiency produced by destruction of valvular tissue. Penicillin is generally the drug of choice. Although the microorganism was sensitive to this agent, unfortunately the patient was allergic to it. Under these circumstances, administration of penicillin, even when used in conjunction with adrenal steroids, is of high risk. The choice of antibiotics prescribed for this patient was reasonable, although streptomycin was given for only a brief period. Perhaps some would have employed a combination of antibiotics, adding another to which the organism was sensitive, probably choosing a bactericidal agent.

As mentioned earlier, even after eradication of the infection, death is sometimes produced by uncontrollable heart failure resulting from destruction of valvular tissue, but that did not appear to be the course here. The patient had angina relieved by nitroglycerin and died suddenly, suggesting involvement of the coronary arteries. Bacterial endocarditis of the aortic valve is the most common cause of coronary embolism, and this appears to be the most probable course of events in this patient. Furthermore, it is likely that the cardiac arrhythmias thought to be due to digitalis sensitivity earlier in the hospitalization were really caused by coronary emboli originating from the vegetations located on the aortic valve. Embolism is not related to the success of antibiotic therapy since it can occur for some time after the infection has been eliminated.

In conclusion, I believe that this patient had calcific aortic stenosis, probably on a congenital basis, with a bicuspid or unicommissural valve. The valve was insufficient after, and probably also before, the onset of acute bacterial endocarditis. Although the patient was treated for six weeks, she had angina pectoris and died suddenly, probably from coronary embolism originating from vegetations located at the aortic valve.

Dr. Michael E. Korns will present the pathologic findings.

Dr. Michael E. Korns:*

At necropsy the principal abnormalities involved the cardiovascular

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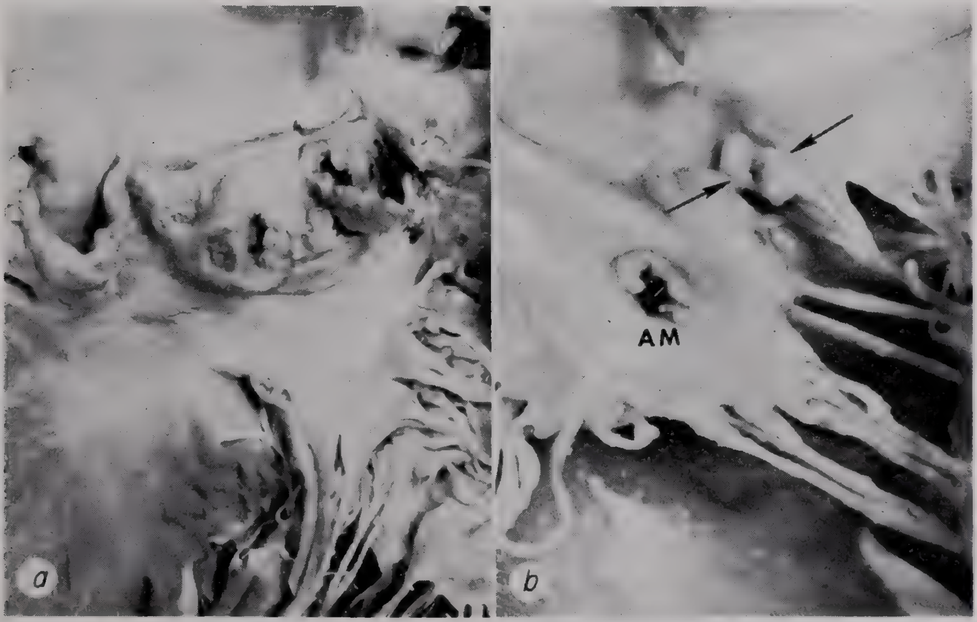

Fig. 4 — Aortic valve and ventricular surface of anterior mitral leaflet. *(a)* Perforation and vegetations of aortic cusps. *(b)* Atrial surface of mitral valve. Perforation of anterior leaflet (AM) and vegetations on posterior medial commissure (between arrows). Vegatations on surfaces of chordae.

Continued

system and, in particular, the aortic and mitral valves. The valvular lesions included chronic rheumatic aortic valvular endocarditis with insufficiency and bacterial endocarditis with perforation of each cusp. Also present were secondary bacterial endocarditis of the mitral valve and acute subendocardial infarction of the anterolateral papillary muscle of the left ventricle.

The heart was hypertrophied, weighing 595 grams. The degree of left ventricular hypertrophy was relatively greater than that of the right ventricle. There was patchy scarring of the left ventricular myocardium. Manifestations of congestive heart failure included generalized vascular stasis and hydropericardium (150 ml.). The aorta showed a severe degree of atherosclerosis.

The aortic valve was tricuspid. Each of the cusps was thickened and roughened, and there was a minimal degree of patchy calcification. Each cusp contained at least one perforation, but the posterior cusp contained four (Figure 4(a)). The contact surface of each cusp was surmounted by friable, grayish-tan vegetations. These were largest at the margins of the perforations through which the vegetations were continuous with vegetations on the sinus side of the cusps. The anterior leaflet of the mitral valve in its lower one third contained a perforation which measured approximately 0.5 cm. in diameter (Figure 4(b)). Obscure from the ventricular side of the leaflet (Figure 4(a)), the perforation was evident on the atrial side and was surrounded by vegetations which were similar to the aortic valvular vegetations. Additionally, there were vegetations deposited on the posteromedial commissure of the mitral valve.

The contiguous chordae tendineae had a ragged, lusterless appearance, and several were surmounted by small, yellowish vegetations. The mitral "ring" showed a small degree of calcification. There were jet lesions in the endocardium of the left ventricle; most of these were plaque-like, but several, in the central one third of the septum, took the form of small diastolic pockets (Figure 5).

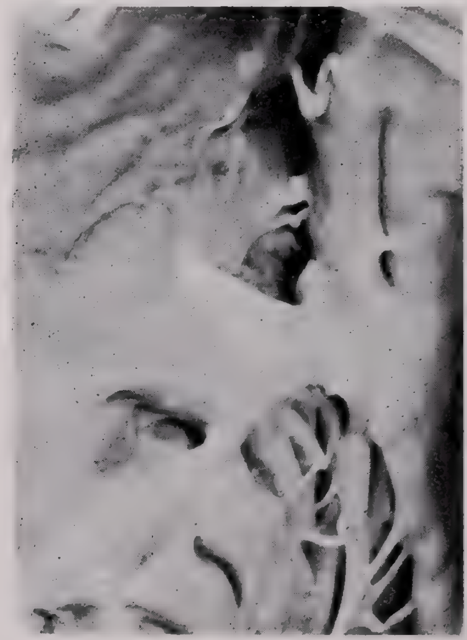

Fig. 5 — Endocardium of left ventricle. Endocardial pocket resulting from chronic aortic insufficiency.

The myocardium of the left ventricle, including the papillary muscles, showed patchy scarring, and the anterolateral papillary muscle was a mottled yellow; the gross appearance suggested acute infarction. The coronary arteries showed minimal atherosclerosis, and no coronary emboli were demonstrated either grossly or microscopically.

Histologically, the distortion of the aortic cusps was readily apparent (Figure 6(a) and (b)). The vegetations were engrafted upon cusps which were the seat of thickening with dense fibrous tissue containing small foci of calcification. Clumps of gram-positive bacteria, some of which formed short chains, were found in the aortic and mitral valvular vegetations (Figure 6(c)). Unfortunately, it was not possible to tell whether the organisms were viable. The infection was severe enough, however, to have caused an incipient aneurysm of one aortic sinus (Figure 6(a)) and a microabscess in the wall of the contiguous aorta (Figure 6(b)).

The atrial surface of the margin of the perforation in the anterior mitral leaflet showed nodular, confluent masses of acutely and chronically inflamed granulation tissue (Figure 7(a)), and there were several microabscesses in juxtaposition to the margin of the perforation. The process of infarction involving the anterolateral papillary muscle of

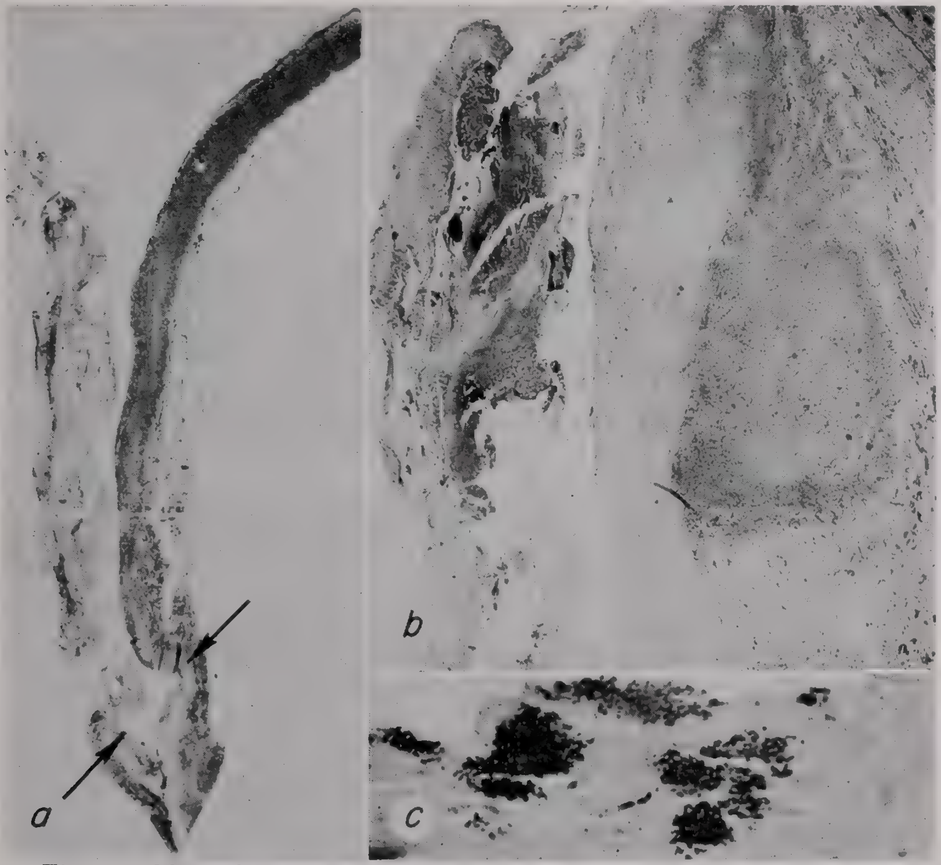

Fig. 6 — Photomicrographs of aortic valve and root of aorta. *(a)* Aortic wall and valvular cusp. The latter is perforated. Vegetations on surfaces of valve. Incipient aneurysm of aortic sinus (between arrows). (Movat stain; ×2.) *(b)* Cusp and segment of adjacent aortic wall. Abscess in wall of aorta and vegetations upon cusp. (H & E; ×8.) *(c)* Gram-positive cocci in aortic valvular vegetation. (MacCallum gram stain; ×430.)

Continued

the left ventricle was quite recent and characterized by extensive areas of necrosis intermixed with viable muscle and small scars. In the majority of areas with necrosis the muscle fibers showed only eosinophilia without cellular infiltration. In other areas infiltration with polymorphonuclear leukocytes (Figure 7 (b)) was present.

Dr. Jesse E. Edwards will give a closing summary.

Dr. Jesse E. Edwards:*

From the pathologic findings and the clinical history it is evident that this patient had suffered from aortic insufficiency of rheumatic origin for some years. The chronicity of the aortic insufficiency is well supported by the fact that the heart was hypertrophied, weighing just under 600 grams. The occurrence of bacterial endocarditis in patients having antecedent valvular disease, often of rheumatic nature, is an accepted phenomenon. It is uncommon, however, that the antecedent disease is sufficient in degree to cause significant cardiac dysfunction. In this regard this patient's case is unusual, since there was evidence of congestive cardiac failure from aortic insufficiency preceding the occurrence of bacterial endocarditis.

The lesions of bacterial endocarditis in this case were characterized by extreme destruction of the aortic valve resulting in aortic insufficiency

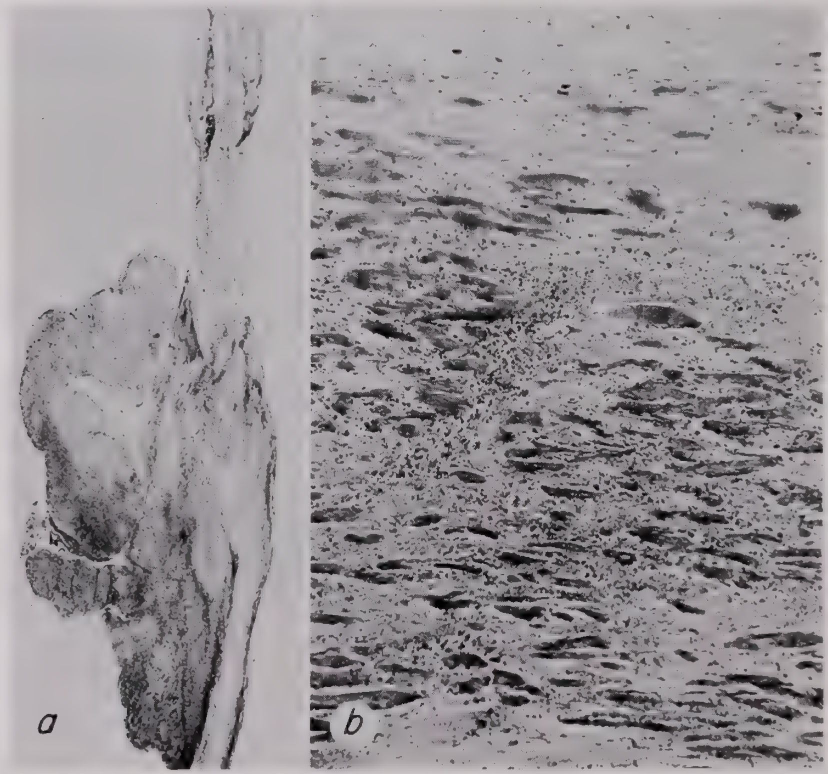

Fig. 7 *(a)* — Photomicrograph of anterior leaflet of mitral valve from section taken just peripheral to perforation shown in Figure 4 *(b)*. Nodular vegetations on atrial surface. (Movat stain; ×7.) *(b)* Anterolateral papillary muscle of left ventricle. Infarction with infiltrate of polymorphonuclear leukocytes. (H & E; ×100.)

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*Director of Laboratories, The Charles T. Miller Hospital, St. Paul, Minnesota; Clinical Professor of Pathology, University of Minnesota, Minneapolis.

on its own account. Coupled with the antecedent aortic insufficiency of rheumatic origin, the degree of incompetence of the aortic valve after the effects of the bacterial endocarditis were added must have been of severe proportion, accounting for significant mechanical disturbances in cardiac function in this patient, even though bacteriologic cure had been obtained. This is one of the tragedies of the present medical era when the patient with bacterial endocarditis may benefit from antibiotic therapy as far as the infection is concerned, but in some cases, as in this instance, the mechanical destruction caused by the active stages of bacterial infection leaves the patient with a serious mechanical defect in one or another cardiac valve.

The mitral valvular lesions in this case are of interest. It will be recalled that there was a perforation in the anterior mitral leaflet and a focus of infection in the posteromedial commissure. Each of these lesions is considered to have resulted from aortic valvular insufficiency, while active infection of the aortic valve was present. Infected blood which regurgitated had impacted against the underlying mitral valve to cause the secondary foci of infection in the mitral valve. In this particular case the perforation of the anterior mitral leaflet was relatively small and of itself did not contribute to any significant cardiac dysfunction. In other cases a similar phenomenon results in a gross defect in a leaflet of the valve. In some cases rupture of mitral valvular chordae may be the significant mitral valvular complication of regurgitation through an infected aortic valve. It is to be emphasized that in some cases of aortic valvular endocarditis the secondary effects upon the mitral valve may be more significant than those upon the primarily involved aortic valve.

The myocardial lesions observed in this case were characterized by acute infarction which was localized in the anterolateral muscle of the left ventricle. When bacterial endocarditis involves a valve in the left side of the heart, embolism of vegetative material into the coronary system is common. This often results in focal, microscopic-sized infarcts of the myocardium. In this particular case the basis for localization of infarction to the anterolateral papillary muscle is not clear. One possibility is that coronary embolism (although no such lesions were observed) was concentrated in the zone that became infarcted.

Drs. Ernesto Arosemena and James H. Moller and I demonstrated that there is a tendency for infarction of the left ventricular papillary muscles in instances of left ventricular hypertrophy, whatever the cause. It is possible that the infarction of the anterolateral papillary muscle observed in our case was a manifestation of this phenomenon. While mitral insufficiency was not demonstrated in our patient, it is possible that this disturbance had in fact been present as a result of the demonstrated involvement of the anterolateral papillary muscle of the left ventricle.

It will be recalled that calcification of the aortic valve was described during the roentgenoscopic examination. Although calcific foci were found in this valve during the pathologic examination, the degree of such involvement seemed inadequate to have been visible by roentgenoscopic examination. Also, it is questioned whether the minor degree of

Continued

calcification of the mitral "ring" could have been visible and so confused with aortic valvular calcification.

Final Anatomic Diagnosis

Rheumatic aortic valvular insufficiency with complicating bacterial endocarditis.

Francis J. Everhart, M.D.*
James N. Karnegis, M.D.*
Michael E. Korns, M.D.*
Jesse E. Edwards, M.D.*
St. Paul, Minnesota

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*From the Departments of Medicine and Pathology, The Charles T. Miller Hospital, St. Paul, and the University of Minnesota, Minneapolis.

Old Medical Equipment Needed

Minneapolis People to People are sponsoring a drive for used or repairable medical equipment and supplies which will be sent to Santiago, Chile, the Sister City of Minneapolis.

Equipment will be distributed by the medical faculty of the University of Chile to poor hospitals in the entire country. There is a dire need for any equipment or supplies that can be repaired to a useable condition. Conditions in many areas are such that patients are sometimes placed two to a bed, as in the case of women's confinements. In many cases there is a total lack of hospital facilities.

Doctors are asked to bring the material to the hospitals, which are serving as collection points. If the equipment is too large to be transported, please call Joe Paulson of the Jaycees at Swedish Hospital X-Ray department (333-4171) in Minneapolis.

Surgical Meeting

A dinner meeting of the Minneapolis Surgical Society will be held December 1 at the Minneapolis Club in Minneapolis at 6:00. The following speakers will be guests of the Society for that evening:

George C. Hottinger, M.D. — "Cushing Syndrome — Surgical Perspective With Report of a Case"

Michael F. Lynch, M.D. — "The Typical, Atypical, and "Atypical" Ductus Arteriosus in Infants and Children. Surgical Consideration in 23 Consecutive Cases"

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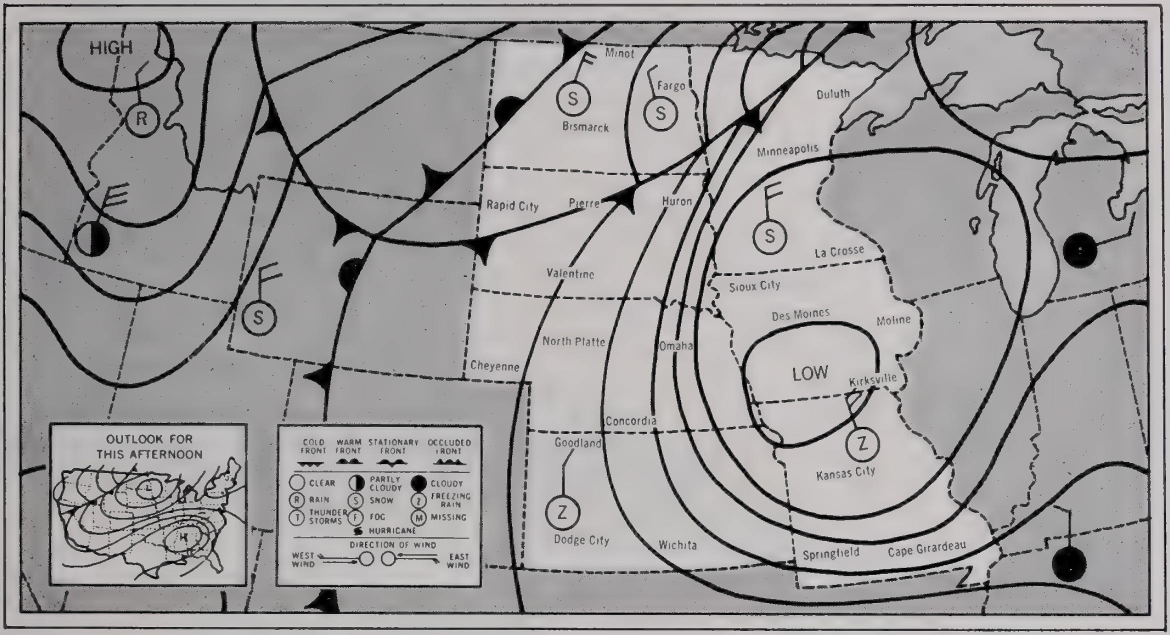
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Complications of Stapedectomy

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USUALLY STAPEDECTOMY is a very successful surgical operation, but occasionally complications occur that tax the surgeon and distress the patient. These complications may be divided into those that are apparent during the surgical procedure and those that are manifest in the postoperative period.

Complications Apparent During the Surgical Procedure

Bleeding

Excessive bleeding can make stapedectomy a difficult and miserably prolonged procedure. The cause of the problem may be hypertension, either primary or due to anxiety, an excessively prolonged operation, or an unsuspected blood dyscrasia. Otosclerotic foci in the young person or in any person in whom there is highly active otosclerotic disease are inclined to bleed excessively. These problems are more easily forestalled than treated, once they have been allowed to develop. Adequate premedication to allay anxiety, a properly placed circumferential canal-skin injection of lidocaine and 1:100,000 adrenaline, restriction of operating time to less than 45 minutes, and full use of suction irrigation and diamond-dust burrs for bony bleeders are all advised.

Injuries and Abnormalities of the Incus and Malleus

The most common ossicular injury sustained during stapedectomy is dislocation of the incudomalleal* joint. Dislocation is caused either by poor control of the curette when bone from the posterosuperior canal wall is removed or by uncontrolled manipulation within the middle-ear cavity. Sometimes the dislocation may be reduced from below; at other times[1] the epitympanum must be exposed further and the incus replaced in its correct articulation.

Abnormalities of the incus and malleus are uncommon. They include absence of the long process of the incus (usually destroyed by infection), absence of the entire incus, and fixation of the head of the malleus to the roof of the epitympanum by a bony spur. The partial or complete loss of the incus presents the operator with the problem of where to attach the strut of the prosthesis. Usually the surgeon compromises successfully by attaching the strut to the handle of the malleus. Routine assessment of the mobility of the ossicular chain should enable the recognition of a fixed mallear head.

Problems at the Footplate

The "Floating Footplate."—During the removal of the superstructure of the stapes, the footplate sometimes becomes mobile and free. In this situation the footplate resists attempts at removal by shifting away and causing waves of pressure in the perilymph, thus damaging the inner ear. To deal with this problem, House[1] advised that, with a fine sharp needle, a small hole be made in the footplate prior to removal of the superstructure. The hole prevents traumatizing suction on the membranous labyrinth during elevation of the footplate. A thicker footplate may be impossible to perforate with a needle; in this case, extremely cautious use of a footplate drill is necessary.

The "Obliterated Footplate."—Here the annular ligamentous margins of the stapes may be obscure and the otosclerotic over-

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*See Test Your Word Score Page 1719.

growth marked. More commonly, the margins of the ligament may be distinct and the footplate not too abnormal. It is fortunate that the obliterated footplate is uncommon, because after stapedectomy the incidence of postoperative sensori-neural hearing loss and regrowth of otosclerotic foci with secondary closure of the oval window are discouragingly high.

McGee[2] stated the belief that obliterated footplates are handled best by drilling a small hole in the center of the footplate and inserting a stainless-steel piston. House[1] advised not to remove areas of otosclerosis that abut on the promontory, the facial nerve, or the sides of the oval window. He believes, as do many others, that otosclerosis is activated by trauma. If the footplate of the stapes has previously been operated on and bony closure is discovered at a subsequent operation, a secondary removal of the "footplate" is considered so likely to produce cochlear loss that many surgeons advise that no further surgery be performed on the footplate.[1,3]

Free Footplate Fragments.—The footplate may break up during removal, and a fragment or sometimes an entire footplate may drop into the vestibule. Tiny fragments are usually not a concern, but expert opinion is divided on what to do about large ones.

In their experience, Cawthorne[4] and Portmann[5] found that if large fragments are left in the vestibule very poor hearing usually results. House[1] believed that large fragments cause no more than persistent positional vertigo.

A fragment large enough to be seen probably should be removed, but blind probing seems far too likely to cause permanent damage to the inner ear to be advised. Manipulation in the vestibule should always be stopped if vertigo occurs.

Anthony[6] pointed out that the white utricular macula deep to the superior rim of the oval window may simulate a bone fragment. Naturally, it is disastrous to remove this "fragment."

Profuse Perilymph Leakage

This is an unusual event. In extreme cases, perilymph gushes from the oval window and fills the middle ear and sometimes even the external auditory canal. The etiologic possibilities include a large cochlear aqueduct, a fissure in the otic capsule, and a fracture of the lamina cribrosa* with an instrument. Shea[3] reported 17 instances of such leakage in a series of 780 patients. The condition is usually controllable at surgery by Gelfoam packing plus muscle or vein packing as well. Coverage with antibiotics for five to seven days afterward is strongly recommended. Cawthorne[7] advised reoperation if the perilymph drainage has not ceased within a few days after operation. Patients with excessive perilymph leakage during operation possibly are more likely to have a footplate fistula later. These patients should be closely followed and, if an infection of the upper respiratory tract develops, treatment should be vigorous because of the potential danger of labyrinthitis.

Complications Apparent in the Postoperative Period

Disturbances of Taste and Oral Sensation

There is a surprising lack of agreement as to how troublesome the symptoms are that result from injury of the chorda tympani nerve during stapedectomy. House[1] stated that sectioning, partial tearing, or even stretching of the chorda tympani may cause the common postoperative symptom of metallic taste on the anterior two thirds of the tongue or soreness or dryness of the mouth. These symptoms usually subside in three to four months.

Bull[8] reported that unilateral section of the chorda tympani resulted in 32% of 126 patients having persistent symptoms of metallic taste or soreness after one year, whereas only 7% of 100 patients had persistent symptoms at the end of one year when the chorda tympani had been preserved. He believed that the common practice of sectioning the suspected stretched nerve to avoid troublesome oral discomfiture was irrational, as such discomfort rarely occurred after nerve stretching. He stressed that 78% of patients in his series had permanent symptoms if both chorda were cut. These patients have dry mouth and total lack of taste on the anterior two thirds of the tongue. There are no known cases of the taste buds originally supplied by the chorda tympani nerve being reinnervated by the glossopharyngeal nerve. Thus, every effort should be made to preserve the chorda tympani nerve, especially if the opposite one has previously been sectioned.

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*See Test Your Word Score Page 1719.

Equilibrium Disturbances

These do not appear to be a common problem, according to the reports of most otologists, although the patient has a period of hesitancy when moving his head suddenly and has slight imbalance when walking; this occurs after even the most atraumatic stapedectomy and clears quickly.

Shea[3] discussed another entity — postural giddiness after stapedectomy. The patient finds that tilting his head backward or somewhat to the side causes violent transitory vertigo. Shea believed that this is utricular in origin and could possibly be caused by a bone fragment irritating the utricle. Shea[3] believed that aviators, steeplejacks, and others who require a perfectly functioning vestibular labyrinth to do their jobs need to be warned, before operation, of this risk.

A prosthesis that is too long is a well-known cause of postoperative, persistent equilibrium dysfunction. House[1] suggested that the distance between the footplate and the incus be measured routinely and that the prosthesis be tailored accordingly.

Problems of Infection

Otitis media occurs occasionally after stapedectomy. Routine postoperative treatment with antibiotics probably suppresses otitis media that might otherwise occur. Several instances of meningitis, sometimes months after stapedectomy, have been reported, and there have been a few consequent fatalities. Preceding the onset of meningitis, the patient often has had a head cold and has created a situation whereby increased intratympanic pressure — such as flying, driving a car in the mountains, underwater diving, or blowing the nose vigorously — has caused rupture of the foot plate prosthesis, with the subsequent ingress of contaminated material from the middle ear. Shea[3] has reported a case of mastoiditis from *Proteus* organisms and of subsequent jugular foramen syndrome* after a stapes-mobilization procedure in the presence of external otitis. After a stormy course, the patient recovered.

According to House,[1] the tympanic membrane ruptures before the Gelfoam-based, oval-window membrane does when infected material is present in the middle ear. This is a fortunate event and prevents otitis media from being a very dangerous complication of stapedectomy.

To decrease the possibility of otitis media after stapedectomy, diving and unpressurized-air travel should not be permitted, although swimming and pressurized-air travel can be.

Anthony[6] emphasized that an ounce of prevention with scrupulous preoperative preparation of the ear canal and exacting operative technique is worth a pound of cure. Wright and Marmesh[9] have had only one case of otitis media in 2,749 cases of stapedectomy, after preoperatively treating the canal skin with iodine.

Facial Nerve Palsy

Facial nerve paralysis occurring after stapedectomy is rare. The palsy may be caused by trauma or by the local effect of lidocaine upon an exposed facial nerve within a dehiscent facial canal. In the latter instance, the function of the muscles of the face should completely recover within the first six hours after operation.

The function of the facial nerve must always be assessed immediately after stapedectomy, because if the function is normal and a palsy develops later, the treatment is different from that advocated if paralysis is noted at the end of the operation and is unchanged after a period of six hours' observation.

A delayed palsy commonly is partial, and recovery usually occurs in one to three weeks. The pathologic process underlying it undoubtedly is neurapraxia. A patient

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*See Varnet's Syndrome Page 1676.

with this type of paralysis should be observed and not immediately reoperated on.

The immediate postoperative palsy may be handled conservatively, too, but only if the operator is sure that he did not severely damage the facial nerve. Most surgeons usually are not certain, however, of the extent of the injury that causes an immediate postoperative palsy, and when doubt exists they advocate early exploration of the facial nerve. An impacted bone chip or a hematoma may be the cause of the palsy; the remedy is removal. When the nerve has been severed, it may be possible to approximate the ends. Nerve grafting is indicated if a gross breach in the continuity of the nerve exists.

Subsequent Hearing Losses

These losses are often classified as either immediate or late, but perhaps can be grouped more informatively as conductive losses or sensori-neural losses.

Conductive Losses

These are nearly always caused by technical errors. The prosthesis may slip off the long process of the incus if the attachment is loose. A prosthesis that is tightly attached to the incus may cause incudal necrosis and subsequent disruption of the ossicular chain. Polyethylene struts were particularly bad in causing incudal necrosis and are not used now. A prosthesis that is too short prevents an effective oval-window seal, and a conductive loss results. Conductive losses that occur in the early postoperative period are usually due to the reactionary serous otitis that is so often seen after stapedectomy or tympanotomy. In reactionary serous otitis, awaiting the resolution of the fluid is regarded as the best decision. Myringotomy and suction removal of the fluid is advocated by House,[1] if the conductive loss is persistent. Later in the postoperative period, bony reclosure of the oval window or, rarely, calcification in the graft material may cause a delayed conductive loss.

Sensori-neural Losses

Immediately after stapedectomy, minor degrees of high-tone, sensori-neural loss that are not permanent are probably due to slight trauma to the hair cells of the organ of Corti. Severe to complete sensori-neural hearing loss, although embarrassing to the surgeon and unfortunate for the patient, does not occur often. Cody and associates[10] reported that 1.9% of their 639 patients had profound sensori-neural loss six months after operation. These patients were operated on between 1960 and 1963. By far the lowest incidence of severe sensori-neural loss was reported by Hough.[11] He has performed partial stapedectomy and believes that lack of trauma associated with this technique explains his excellent results.

Much statistically based discussion and rather less animal experimentation have led to the incrimination of the following factors as contributory to profound sensori-neural loss: trauma, infection, bleeding, bone chips or dust, graft material, any revision operation, "drill-out" operations, stapedectomy after fenestration, extremes of age of the patient, and loss of the stapedius reflex.

Trauma has been suggested as a cause because the incidence of sensori-neural loss decreases as the operator gains experience. Experimentally, Schuknecht and Tonndorf[12] have shown that excessive manipulation of stapes can result in injury to the organ of Corti in the upper basal turn of the cochlea of the cat, thus creating a lesion identical to that from a high-intensity blast or head injury. Hohmann[13] demonstrated that direct trauma to the membranous labyrinth in the vestibule often results in widespread labyrinthine reactions; the reactions vary from mild labyrinthitis to a severe reaction that is followed by invasion of the labyrinth with connective tissue and bone.

Shea,[3] in support of the theory that infection causes labyrinthitis and sensori-neural loss, stated that a large percentage of ears with such loss had, at repeat operation, massive adhesions in the oval window niche around the graft and the prosthesis.

House[1] believed that blood in itself does not cause cochlear hearing loss. Bleeding, however, may lead to further surgical trauma by poor visualization, longer operating time, and prolonged use of suction. Hohmann[13] has shown that blood can be injected into the inner ear of cats without inner-ear complications. Shea[3] has noted that, whether bleeding is a cause or an effect, profuse bleeding occurs more often in ears that undergo further cochlear loss.

While at one time it was believed that bone dust or chips probably could prove irritating to the cochlea and cause sensori-neural loss[14] by a theoretic interreaction of labyrinthine fluid and bone protein and inorganic ions, it now seems generally agreed that bone chips do not cause inner-ear damage provided they do not injure the membranous labyrinth mechanically.

The possibility of a graft material such as a Gelfoam prosthesis being more likely than other graft materials to perforate and cause a fistula, resulting in inner-ear infection and subsequent hearing loss, has been refuted by House's[1] excellent results with this material.

Although fat, vein, and fascia have been used extensively in previous years, there has been a trend to use Gelfoam more and more as the graft material to cover the oval window. The switch was based in part on the better results obtained by surgeons who used Gelfoam than by those who used tissue material. Theoretically, too, Gelfoam can be kept sterile more easily than can fat, fascia, or vein. Toxic products of degeneration from the fat, fascia, or vein and a foreign protein reaction have been postulated as causing hair-cell damage.[15] In experiments recently performed on cats, however, Hayden and McGee[16] could not definitely incriminate any factor in fat grafts. The final answer to the question of the superiority of Gelfoam as compared to tissue grafts will be found in the results of the long-term, follow-up studies of the use of Gelfoam by the average otologist.

Shea[3] reported that 11.1% of 61 patients had cochlear loss at a one-year follow-up of a series of repeat operations on the same ear with Teflon. Other surgeons had cited similar experiences with revision operations.

After primary "drill-out" procedures for obliterative otosclerosis, Shea[3] found a 10% incidence of profound sensori-neural loss in 186 patients at the end of three years. Recently, Sooy and associates[17] reported that four (6.3%) of 64 patients had a discrimination loss of as much as 10% four months after "drill-out" procedure.

Shea[3] reported a 9.1% incidence of cochlear loss after stapes surgery that followed earlier fenestration. He believed that the added trauma of a secondary operation as well as infection from the mastoid bowl are both causative factors.

Shea[3] cited appreciably higher incidences of sensori-neural loss in patients at the extremes of life. The reason for this is not definitely known.

Exposure to loud noise after loss of the damping effect of the stapedius muscle through its routine section at stapedectomy theoretically entails a greater risk of sensori-neural loss. Cawthorne[7] advised the wearing of cotton wool or ear plugs during exposure to loud noise for several weeks or months after stapedectomy.

Summary

In summary, complications are associated with stapedectomy, but these are usually minor. The dreaded problem of further sensori-neural hearing loss is nearly always associated with excessive surgical trauma. Long-term follow-up studies to determine the best techniques along with careful planning and attention to surgical detail should improve the percentage of successful results.

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Rochester, Minnesota

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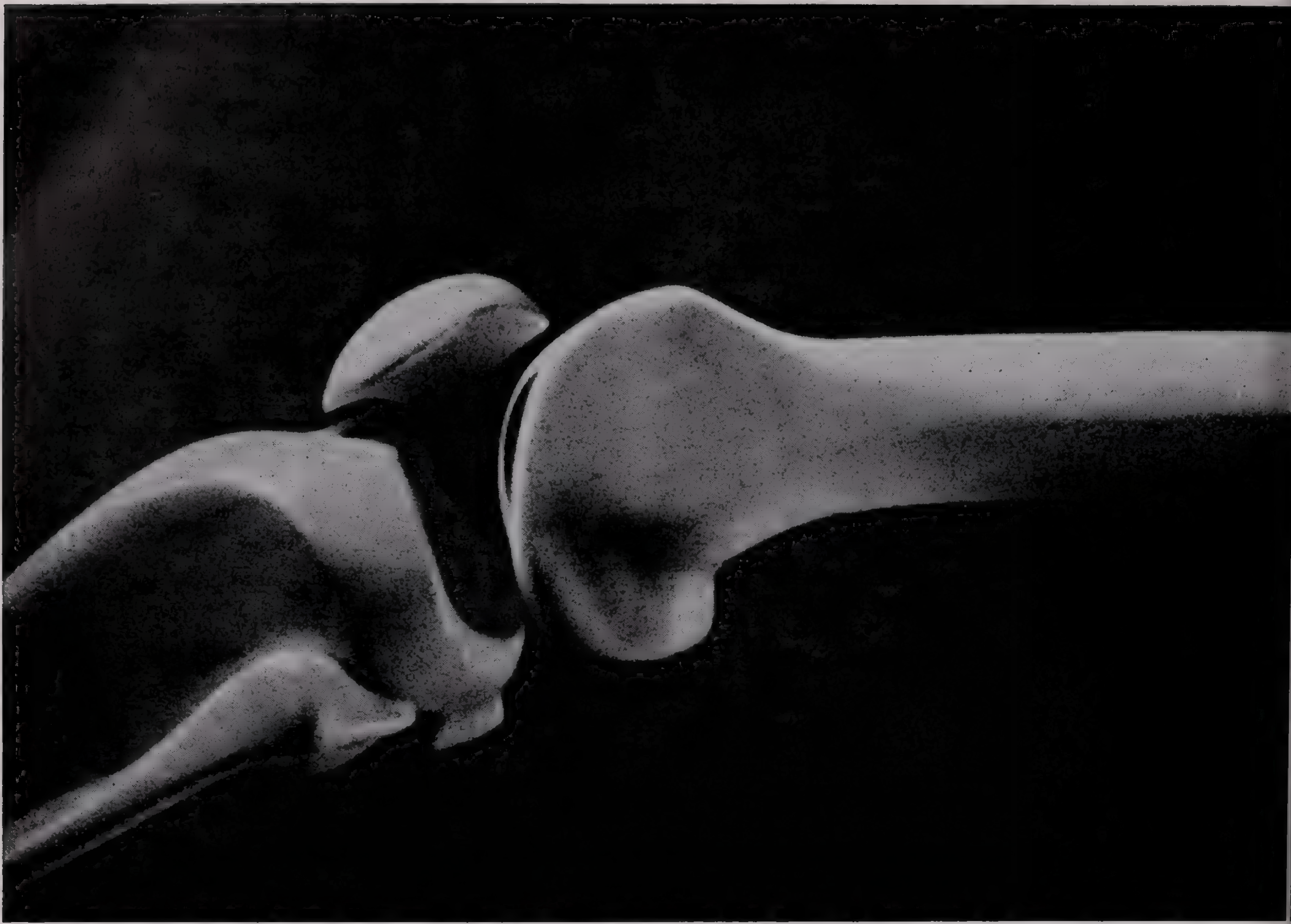
4-17 May be secured from the author or the reprints.

The Democratic party is like a mule — without pride of ancestry or hope of posterity. — Emory Storrs, 1888.



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The most common adverse reactions are nausea, edema and drug rash. Moderately lowered red cell count may sometimes occur due to hemodilution. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. Infrequently, agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome or a generalized allergic reaction may occur and require withdrawal of medication. Stomatitis, salivary gland enlargement, vertigo or languor may occur. Leukemia and leukemoid reactions have been reported but cannot definitely be attributed to the drug. Thrombocytopenic purpura and aplastic anemia are also possi side effects.

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Grand Rounds

Inappropriate Secretion of Antidiuretic Hormone[*]

ROGER STENLUND, M.D.
Medical Resident

HYPONATREMIA[**] IS encountered frequently in clinical medicine. This finding in itself has little value unless correctly interpreted in light of accompanying data.

Hyponatremia usually occurs in three main settings:

a. Hyponatremia associated with circulatory insufficiency and an overexpanded extracellular fluid volume. Congestive heart failure, the nephrotic syndrome, and severe hepatic disease are examples.

b. Hyponatremia with circulatory insufficiency and a contracted extracellular fluid volume, as may be seen with overzealous diuretic therapy, severe gastrointestinal electrolyte losses, excessive perspiration losses, renal disease and adrenal failure.

c. Hyponatremia associated with an adequate circulation and an expanded extracellular fluid volume.

The latter situation is of major interest in this paper as it exists in two circumstances — the syndrome of inappropriate antidiuretic hormone secretion and its experimental prototype of prolonged administration of exogenous antidiuretic hormone and water.

Antidiuretic Hormone

Neurohypophyseal extraction yields a relatively pure protein with a molecular weight of 30,000, which can be divided into antidiuretic hormone and oxytocin. Both are octapeptides with antidiuretic hormone being arginine — vasopressin, the antidiuretic hormone common to all mammals except swine.

Antidiuretic hormone is probably produced in cells of the supra-optic and paraventricular nuclei and liberated from the terminations of axons of the supra-optico-hypophyseal tracts in response to impulses from these same nuclei or elsewhere in the hypothalamus.[1]

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[*] Presented as a Medical Grand Rounds at Hennepin County General Hospital, May 17, 1966.

[**] See Test Your Word Score Page 1719.

Continued

The Normal (Appropriate) Schema of Antidiuretic Hormone Secretion and Action

Extracellular fluid osmolarity and perhaps also extracellular fluid volume appear to be the most important of the many factors regulating ADH secretion. Changes in extracellular fluid osmolarity of as little as ±2% are postulated to be sensed by osmoreceptors located somewhere within the distribution of the internal carotid arteries, perhaps in the supra-optic nuclei themselves. In response to increased tonicity antidiuretic hormone is liberated and with decreased tonicity the converse occurs. Impulses from volume receptors within the thorax may also influence the release of antidiuretic hormone.

Antidiuretic hormone is liberated in response to many other stimuli, including pain, fear, syncope, apprehension, exercise, smoking, and various drugs — central nervous system depressants (especially morphine, ether, and the barbiturates), nicotine, epinephrine, histamine, acetylcholine, and adenosine-triphosphate.

Likewise, antidiuretic hormone release is inhibited by several factors: alcohol, left atrial distention, hypnotic suggestion of water drinking and conditioned-reflex diuresis.

This variety of factors implies the presence of a central integrative mechanism which receives and integrates these various impulses and then relays stimulation or inhibition of antidiuretic hormone release.

Three Direct Renal Effects:

a. To increase the permeability of the distal convoluted and collecting tubules to water.

b. To stimulate the transfer of sodium into the renal interstitium at the loops of Henle.

c. To regulate the rate of medullary and papillary perfusion by the vasa rectae.

The cumulative effect augmenting water reabsorption and inhibiting excretion of free water. Under maximal stimulus, the urine may reach an osmolarity of approximately 1,400 mOm-L or 3-5 times that of serum.

The basic action of antidiuretic hormone is, therefore, to maintain the osmolarity of body fluids within close limits — i.e. 290 ± 10 mOm/L for serum.

Mechanism for Maintaining Body Fluid Osmolarity:

a. Afferent impulses — probably from several sites in response to several stimuli.

b. A central integrative mechanism assimilating these impulses.

c. The neurosecretory mechanism responsible for antidiuretic hormone.

d. Renal effect or mechanisms which govern water excretion accordingly.[1,2,3]

Syndrome of Inappropriate Secretion of Antidiuretic Hormone

Background Material

Early data by Leaf et al.[5] provided evidence that electrolyte deficit induced by antidiuretic hormone was probably a reflection of water retention more than urinary loss.

Jaenike and Waterhouse[6] found that with a high fluid intake with steady sodium intake (approximately 110 mEq/day) there occurred an initial rapid expansion of total body water associated with an excessive urinary excretion of sodium. After the sixth day of this response, urine osmolarity slowly decreased, urine volume increased and body water balance was reestablished with a concomitant decrease in natruresis,* but with a continuing state of over-expansion of body fluid volume. In spite of continued antidiuretic hormone and water, a new steady state was achieved characterized by persistent overhydration and hyponatremia. This suggested that duration of the overhydrated state was a critical factor in an apparent renal unresponsiveness to continued antidiuretic hormone. This never occurred prior to the seventh day of antidiuretic hormone and water administration. Urine osmolarity progressively fell from a high on day one of 800 mOm/L to values only slightly hypertonic to plasma. Sodium excretion decreased to the point that positive sodium balance was achieved. There was a subsequent three-day period of water retention with value series identical to those obtained during the initial response. Despite continued vasopressin at higher doses, water balance was again achieved at a body weight approximately 5 kg. greater than control weights.

A variant study, similar to the above but with sodium restriction (approximately 32 mEq/day), revealed a similar response pattern, but natruresis was less marked.

These subjects experience mild nausea and headache during periods of maximal water retention, and one had mild ankle edema.

In a subsequent study it was observed that water retention and natruresis were directly related to water intake — being slight at 1,000 cc/day and marked at 2,000 cc/day. On two occasions they were able to achieve net loss of water by the use of mannitol.* In the latter study after periods of lower fluid intake, the urine became actually hypotonic to plasma, whereas in the first study, urine osmolarity was persistently greater than that of plasma. Sodium excretion also tended to parallel sodium intake, but natruresis could not be abolished by sodium restriction alone.

Additional studies allowing intake of 3,150 cc/day had to be discontinued because of severe nausea, vomiting, headache and lethargy.

The occurrence of decreasing urine tonicity associated with a stable but overhydrated state suggests that a state of overhydration could exist without a true, significant sodium-losing state.

They concurred with Leaf that the hyponatremia was due to dilution more than to sodium loss.

The Clinical Syndrome

In the majority of cases the syndrome of inappropriate antidiuretic hormone is entertained after the incidental finding of hyponatremia. The syndrome should be considered strongly with the preliminary data of hyponatremia, absence of edema and normal blood urea nitrogen. The diagnosis can then be pursued in a more definitive manner. Since there is no readily available and accurate method of antidiuretic hormone measurement, the diagnosis is primarily inferential, initially resting upon the clinical picture and supporting laboratory data and finally upon a response

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*See Test Your Word Score Page 1719.

Continued

to management consistent with that anticipated with the syndrome of inappropriate secretion of antidiuretic hormone.

Several features of this syndrome are characteristic:

a. Hyponatremia without evidence of vascular collapse or significant edema.

b. Extracellular fluid volume usually greater than normal.

c. No evidence of renal or adrenal malfunction.

d. Tendency to increased glomerular filtration rate and low or normal blood urea nitrogen.

e. Urine osmolarity usually consistently greater than serum osmolarity.[7,8]

Differential Features

The initial differential diagnosis includes the other causes of hyponatremia previously mentioned and should pose no difficulty. Probably the most difficult differential is the stage of adrenal insufficiency in which the water-excreting defect is more profound than the salt-losing defect, leading to hyponatremia without apparent body-fluid volume contraction. This may occur, for instance, in non-addisonism patients who are taking steroids for asthma, rheumatoid arthritis, etc., and then have abrupt discontinuance of steroid.[9] In the interests of a definitive diagnosis of this syndrome specific endocrine function and renal function and fluid space determinations should be performed.

Pathophysiology and Other Features of This Syndrome

The "inappropriateness" relative to this syndrome is the secretion of antidiuretic hormone or at least a state of antidiuresis in the absence of the previously mentioned "normal appropriate" stimuli.

Conditions similar to those features of this syndrome have been reported with many disease states, most of which have been intrathoracic or intracranial.

Intrathoracic Diseases:

Neoplasms — majority are oat-cell carcinoma.

Tuberculosis.

Williams et al.[10] published data from a case of oat-cell carcinoma involving the hilum of the lung associated with this syndrome. Utilizing special histochemical staining techniques, they found morphologic changes in the cells of the hypothalamic nuclei and posterior pituitary which were considered indicative of neurosecretory exhaustion due to prolonged secretion of ADH. They do not comment on the possibility that these changes might indicate some other functional state, such as decreased neurosecretory function due to an ectopic secretory focus. Cell counts of the anterior pituitary were felt to be indicative of enhanced adrenocortical activity, and bilateral adrenal hyperplasia was found at autopsy. Adrenal function studies were said to be normal.

Amatruda et al.[11] performed bio-assay techniques for antidiuretic activity on portions of an oat-cell carcinoma from a patient who had exhibited the syndrome of inappropriate antidiuretic hormone. They found an average activity of 212 U.S.P. micro-units of arginine — vasopressin equivalence per mg. of dried tumor. This amount was small compared with that present in normal antidiuretic hormone neurosecretory sites, but they felt that the large total mass of the tumor may have produced functionally significant amounts. Of interest is that they also assayed the activity of tissues from patients with diseases associated with inability to excrete a water load. Tissue from a patient with cirrhosis was inactive. However, hilar lymph nodes from a patient with a demyelinating disease of the central nervous system contained 53 antidiuretic hormone-activity units/day. Hilar lymph nodes from patients with carcinoma of the prostate and sarcoidosis also revealed 20 and 50 antidiuretic hormone-activity units, respectively. Tissue from other cases was negative.[13,6] Histochemical studies as mentioned above would have been of interest in the patient whose tumor demonstrated antidiuretic hormone-like activity. It is not known if the demonstrable activity was due to actual antidiuretic hormone production or to other possible explanations such as an active polypeptide with its own antidiuretic action, or to release of antidiuretic hormone from the bioassay animal (not hypophysectomized) or perhaps ab- or adsorption of antidiuretic hormone by the tumor.

Diseases of, or Including the Central Nervous System:

Neoplasm.
Vascular disease.
Head trauma.
Malformation.
Undiagnosed.
Meningitis.
Metabolic.
Myxedema.
Porphyria.

Vogel et al.[12] specifically attempted to evaluate aldosterone responsiveness as reflected by urine aldosterone levels in a case demonstrating this syndrome, associated with a cerebral tumor. They found aldosterone levels to be within the normal range at all times and exhibiting a normal response pattern to changes in extracellular fluid volumes.

Very little is known regarding the pathophysiological relationships between these various diseases and this syndrome.

Two cases reported by Carter et al.,[8] both with central nervous system disease (one metastatic tumor and one skull fracture), seemed to exhibit a biphasic pattern. Early in the syndrome antidiuretic hormone secretion appeared to be independent of both extracellular fluid volume and tonicity, as evidenced by prompt excretion of a massive saline load which transiently raised extracellular fluid volume higher and sodium levels to normal. Later, antidiuretic hormone effect appeared less marked in response to volume expansion. This may represent decreased renal responsiveness to antidiuretic hormone as mentioned earlier rather than to actual suppression of antidiuretic hormone as they suggested.

Carter's group and others were able to demonstrate sodium retention in response to small doses of 9-alpha-fluorohydrocortisone. This ability in association with failure to retain a salt load and continued natruresis with a negative sodium balance was suggested as evidence in support of the concept of reduced aldosterone activity and also to confirm the preservation of renal-tubular salt-retaining ability.

This conflicts with the earlier opinion of Peters who, in 1950, presumed

Continued

the underlying mechanism to be renal salt-losing secondary to central nervous system disease, either directly via the renal nerves or indirectly by depressed adrenocorticotropic hormone.

Goldberg[9] felt that, while the exact mechanism of hyponatremia associated with inappropriate antidiuretic hormone is unknown, it may be due in part to two factors: a. Increased glomerular filtration rate, b. Decreased secretion of aldosterone, both directly or indirectly resultant from the increased extracellular volume.

As Leaf has pointed out[7] a small urine volume may not be present during all stages of the antidiuretic hormone syndrome because, after the initial stage of water retention, oliguria and natruresis, two conditions tend to modify continued antidiuresis: (a.) The glomerular filtration rate increases promoting water excretion, (b.) Renal tubular response to antidiuretic hormone is seemingly decreased.

It is observed that after the initial phase, urine volume will closely reflect water intake. This would appear to be a safety mechanism protecting these patients from unlimited over-expansion of body fluid volume.

A case exhibiting a prolonged tendency to inappropriately secreted antidiuretic hormone was reported by Epstein et al.[14] This patient had a persistently abnormal electroencephalogram thought to represent an abnormality of upper brain stem and diencephalon region, but no other neurological disease was evident. For a period of over two years she was managed satisfactorily with serum sodium in 140-145 mEq/L range by instructing her to drink only when thirsty. The inappropriate antidiuretic hormone syndrome was reproduced at intervals in this patient by administration of a water load.

In cases associated with myxedema, the syndrome could not be reproduced after the patient became euthyroid with treatment.[16]

The syndrome has been observed during acute exacerbations of porphyria, but in the interim between attacks, the syndrome could not be reproduced.[17]

Goldberg[9] has summarized some pathophysiologic situations which could be responsible for the inappropriateness of antidiuretic hormone control in this syndrome:

a. A persistent positive stimulus for antidiuretic hormone secretion, such as an irritative lesion within the central nervous system or persistent impulses from receptors within a diseased thorax.

b. Defective ability to maintain inhibition of antidiuretic hormone secretion in response to normal inhibitory stimuli.

c. Re-setting of osmoreceptors to a subnormal level.

d. The multiple possibilities associated with neoplasms.

Treatment

The most important facet of treatment is fluid restriction. In most patients studied, correction was approaching normal by about the third to the sixth day after institution of fluid restriction. Some authors[15] have mentioned supplementary use of mannitol, which increases free water excretion, but is of little consequence compared to fluid restriction. Alcohol was usually ineffective.

Long-term management largely depends on the underlying disease. Success will require a cooperative and intelligent patient.

Prognosis

This also depends on the associated disease process. Some patients reported never achieved fluid balance prior to death. A patient followed for over two years has been mentioned, in whom the antidiuretic hormone defect remains, and in whom the syndrome can be reproduced at will, yet who is subjectively well, providing fluid intake does not exceed that necessary to quench thirst.[14] Reference has been made to the findings in myxedema and porphyria during the treated and symptom-free intervals.

Case Report

An 81-year-old Caucasian male was admitted 1/23/66 to Hennepin County General Hospital in acute respiratory distress. Physical findings were those of chronic obstructive pulmonary disease with an acute exacerbation. There was a history of chronic lung disease for many years with frequent acute episodes, the last in September 1965. He also carried the diagnosis of chronic brain syndrome secondary to cerebral arteriosclerosis and had a diffusely abnormal EEG. with normal cerebral spinal fluid.

Initial treatment consisted of I.V. fluids, bronchodilators and IPPB. On the second hospital day he was felt to be in incipient cardiac failure and was given thiomerin and digitalized without observable change in clinical status. On the fourth hospital day he was found to weigh 166 pounds (15 pounds more than when last discharged), and to have a serum sodium of 122 mEq/L and a urine specific gravity of 1.031. There was no overt edema.

These findings were suggestive of inappropriate antidiuretic hormone syndrome. There was no significant response to infusion of 500 cc. of 5% alcohol, nor any striking response to a mannitol test dose.

Fluid restriction was instituted with subsequent weight loss, rise in serum sodium and modest improvement in overall clinical status. The subsequent hospital course was complicated by his underlying pulmonary disease and obstructive uropathy, but without overt evidence of further fluid and electrolyte imbalance. The patient was discharged from the hospital ambulatory and at his baseline chronic pulmonary and chronic brain syndrome status.

Adrenal function was not assessed. There was clinical evidence of mild congestive heart failure. Renal function was modestly impaired.

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19-22 May be secured from the Grand Rounds Editor.

Well enough for old folks to rise early, because they have done so many mean things all their lives they can't sleep. — Mark Twain

It works.

*What's New in Hematology?**

ALBERT B. HAGEDORN, M.D.**
Rochester, Minnesota

SIGNIFICANT ADVANCES are being made in hematology — equally as impressive as those being made in other fields of medicine. This review will be confined to the clinical or practical advances† and will leave to others the experimental and research advances, which perhaps are more impressive.

Blood Transfusion

Hematologists have always held that many more transfusions of blood have been given than were actually required. This is serious because of the potential hazards associated with the administration of blood. In addition, blood is a precious commodity that must be conserved for therapeutic and economic reasons, research purposes, and national defense needs. We are now beginning to advocate administration of only the specific fraction of blood that is needed by the individual patient. As a result of the improvement and simplicity of the equipment for collecting and separating the component parts of blood, all blood banks can readily fractionate the whole blood obtained from donors. If there is a need for whole plasma, then this alone should be given; if there is a need for platelets, then only platelets should be given; if there is a need for antihemophilic globulin, then only a concentrate rich in this substance should be given; and, if there is anemia requiring transfusion, then only packed erythrocytes should be given. Recently, an analogy has been drawn between the old "shotgun" hematinic therapy and the giving of whole blood, the point being that only the substance lacking should be prescribed. Even infusions of granulocytes are being given in certain cases of leukopenic leukemia to tide the patient over an acute secondary infection or febrile episode. However, this still is not a general practice because it requires a sufficient pool of chronic granulocytic leukemic patients — to act as donors; and the separation of the leukocytes from the other cellular components presents complex technical problems. At the present time this type of transfusion can be done only in large research centers such as the National Institutes of Health.

A practical technique for harvesting antihemophilic globulin from whole plasma has been developed by Dr. Judy Pool at Stanford. It depends on the use of cold temperatures for precipitation of fibrinogen which is rich in factor VIII. Then, by plastic-bag technique, this protein can be removed and the rest of the plasma conserved. This cryoprecipitation of fibrinogen can also be used to concentrate antihemophilic globulin from outdated blood. It has been shown in our laboratory that so-called old blood in the

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*Read at the meeting of the Minnesota State Medical Association, St. Paul, May 16, 1966.

**Mayo Clinic and Mayo Foundation: Section of Medicine.

†I am indebted to Drs. Joseph M. Kiely and E. J. Walter Bowie for some of the ideas mentioned in the text.

Continued

blood bank still contains about 50% of the original antihemophilic globulin that was present when the blood was fresh. We now can make use of this antihemophilic globulin by separating it out by Pool's technique. Another new development is the use of animal antihemophilic globulin concentrates in treating patients with hemophilia and circulating anticoagulants. Most of this experience has been in Europe, but some trials have been made in this country.

Anemia

The reports of the past year indicate that androgen therapy is not as effective as previously suggested for the anemia occurring in the myeloid metaplasia of myelofibrosis and myelosclerosis. In my experience, testosterone has not helped in any such cases. However, in an occasional case of nonhemolytic anemia that may occur in lymphoproliferative syndromes such as chronic lymphocytic leukemia, testosterone has produced some impressive effects. Use of testosterone is also advocated in aplastic anemia, but most results have been poor. Use of testosterone, together with corticosteroids, is also currently advocated for prevention of marrow aplasia when toxic chemical agents are used therapeutically — for example, in conjunction with cyclophosphamide (Cytoxan) or L-sarcolysin (Alkeran) in the treatment of multiple myeloma. The long-acting testosterone derivative, testosterone enanthate (Delatestryl), is given intramuscularly once weekly in a dosage of 600 mg. Impressive remissions of multiple myeloma have occurred with a combined program of L-sarcolysin, prednisone, and testosterone.

Coagulation Defects

Within the past year a new coagulation factor has been officially accepted — factor XIII, the fibrin-stabilizing factor or the Laki-Lorand factor. The new coagulation disorder associated with deficiency of factor XIII has been seen in more than 10 cases. These cases are characterized by severe umbilical bleeding at birth, a condition apparently mistaken for one of the hemophilic states in the past. A case in an adult (31 years old) was also recently recognized. The condition is probably hereditary and occurs in both sexes. All the usual coagulation tests give normal results in these patients. A clot does form, but it is of poor quality. The deficiency is recognized by testing the clot with 5M urea or monochloroacetic acid; normal clots are insoluble in these solutions but, when factor XIII is deficient, the clot readily dissolves. A single transfusion of blood may be effective in preventing further bleeding for as long as two weeks.

The Fibrinolytic States

The dilemma of distinguishing the fibrinolytic states from the consumptive coagulopathies (a new term favored by the coagulationists) has not been solved. There is no single specific test that distinguishes between the two entities and, further complicating the picture, similar clinical conditions may trigger either mechanism. Various causes, such as malignant disease, sepsis, hemolytic transfusion reactions, obstetric complications, and certain pulmonary and pelvic operations, may initiate the production of either a fibrinolysin or a massive intravascular thrombosis or embolization with subsequent depression of many of the coagulation factors. The diagnosis may have to be intuitive. For the fibrinolytic state epsilon-aminocaproic acid (Amicar) is the drug of choice. For the consumptive coagulopathies (often called defibrination syndrome) heparin is the drug of choice. The dilemma is great. Although excellent concentrates of fibrinogen are readily available, administration of fibrinogen alone is not the treatment for some of the consumptive coagulopathies, for example, the one often seen by obstetricians. Because of the deficiencies of prothrombin, factor V, factor VIII, and platelets as well as of fibrinogen, it would be more reasonable to give whole, fresh blood carefully collected in plastic bags rather than fibrinogen alone as is sometimes done.

The Thrombocytopenic States

Thrombocytosis has now been recognized as an occasional complication of malignant disease and may be a worthwhile early clue, when no other signs of the malignant process are evident.

Likewise, thrombocytopenia may occasionally occur with malignant disease, but it is usually associated with what is now called "microangiopathic hemolytic anemia," which results from a variety of disease entities, all characterized by spastic small blood vessels. These changes in the blood vessels lead to changes in the erythrocytes and to anemia similar to the anemia seen after certain heart-valve operations. A clue is the morphologic change in the erythrocytes which are characterized by marked poikilocytosis with frequent schistocytes. This is seen in a variety of conditions, including malignant hypertension, thrombotic thrombocytopenic purpura, systemic lupus erythematosus, polyarteritis nodosa, and metastatic malignancy.

It is feasible to obtain reasonable platelet harvests from whole blood by use of plastic bags for transfusion to patients with thrombocytopenia. However, for the isoimmune thrombocytopenic purpuras with circulating antibodies, platelet transfusions obviously will be ineffective. Steroids are considered to be the drug of choice for acute idiopathic thrombocytopenic purpura (ITP). In chronic ITP, especially in adults, the risk of continued steroid therapy is greater than the risk of splenectomy. For the patient not responding to either steroids or splenectomy, an antimetabolite, such as 6-mercaptopurine or azathioprine (Imuran), can be used as an immunesuppressive agent.

Hematologic Reactions

Although it is well known that drugs are capable of producing adverse hematologic reactions, it is worth emphasizing the point that there is a potential new hazard to the blood with the introduction of each new drug or therapeutic preparation. Every physician should be aware of this potential hazard and should inform his colleagues whenever an unexpected response occurs in a patient.

The recent interest in recognizing the cellular reaction to chloramphenicol (Chloromycetin) bears no relationship to recognizing the adverse fatal reactions that sometimes occur. With the former, the vacuolation of the erythrocyte precursors noted in the bone marrow is directly related to the dose of chloramphenicol, can be predicted, and is reversible if the drug is discontinued in time. With the fatal aplastic anemias and pancytopenias which may occur from chloramphenicol, there seems to be a sensitivity

Continued

reaction involved; this cannot be predicted or prevented and is not related to dose. It probably is related to sensitization from previous use of the drug.

Megaloblastic Anemia

For many years it has been recognized that megaloblastic anemia occasionally develops secondary to anticonvulsant therapy. This results chiefly from diphenylhydantoin (Dilantin) and mephenytoin (Mesantoin), but other anticonvulsant drugs can do this, too. It is now realized that this is an induced folic-acid deficiency state and that patients who develop this anemia need not discontinue the anticonvulsant drug. A therapeutic dose of folic acid is given along with the anticonvulsant.

Hypersensitivity Reaction

In certain cases of chronic myelocytic leukemia treated with busulfan (Myeleran), an interstitial pulmonary fibrosis may develop which, if not recognized early, can lead to the death of the patient. The early signs are cough and wheezing, and a thoracic roentgenogram will show bilateral, fan-shaped pulmonary shadows. The mechanism of this phenomenon is not understood, but apparently it is a hypersensitivity reaction. If the busulfan therapy is stopped early enough, the condition will abate.

Drugs

A new use for an old drug is that of aminopyrine in the treatment of the debilitating febrile reactions that may occur in patients with lymphoma, especially Hodgkin's disease. This is used particularly in cases in which the bone marrow will not tolerate any more specific treatment and high fever persists. The new drug indomethacin (Indocin) is equally effective in this respect and may be the drug of choice.

Recently, 6-mercaptopurine has been shown to have a favorable effect in controlling Waldenström's hyperglobulinemic purpura. However, this is a relatively benign condition and I would think a woman would have to have a strong desire to be rid of her discolored legs before I would be willing to give her such a potentially toxic substance.

In Waldenström's macroglobulinemia, a malignant condition entirely different from the aforementioned state with the same eponym, chlorambucil (Leukeran) has proved to be very effective in controlling the signs and symptoms. Dr. Edwin Bayrd of the Mayo Clinic first used this in treating Waldenström's macroglobulinemia and has been successful in more than 25 cases. Plasmaphoresis has been effective in managing the distressful complications caused by the hyperviscosity syndrome that sometimes occurs in Waldenström's macroglobulinemia and less frequently in multiple myeloma. The condition can be verified by a simple laboratory test: measuring the serum viscosity index by means of a capillary viscometer. After the abnormal globulin has been removed from the plasma by differential centrifugation, the remaining plasma is returned to the patient along with the cellular elements of the blood.

A new chemotherapeutic agent has been added to the armamentarium for treatment of Hodgkin's disease. It is a methylhydrazine derivative marketed as Natulan: a cytotoxic agent whose exact mechanism of action is not known. It is of a different class than the other presently used agents and, therefore, can be given when these other agents have reached their limitations of clinical usefulness.

A new attitude toward Hodgkin's disease has developed recently. Efforts are being made to stage the disease accurately because many radiologists and hematologists think that stage I Hodgkin's disease is now potentially curable. Stage I Hodgkin's disease is defined as one in which the disease is limited to one anatomic region or to two contiguous anatomic regions on the same side of the diaphragm. Although clinical examination in cases of Hodgkin's disease is relatively simple and accurate, it often fails to reveal the status of the iliac and retroperitoneal regions. As a result, if a patient is considered to be probably in stage I, it is mandatory that a retroperitoneal lymphangiogram be made. With present methods this is a simple, low-risk procedure that can be done on an outpatient basis, with results available within 24 hours. If the retroperitoneal lymphangiogram is negative, then high-dose obliterative radiation is given to the localized peripheral nodes.

Diagnosis

Finally, a new, simple, rapid, and apparently reliable test for detecting heterophil antibodies of infectious mononucleosis in serum is now available. It depends on a commercial reagent developed by Wampole Laboratories (Stamford, Connecticut) and called the Mono-Test. Reports indicate an overall accuracy of 99% with no false-negative results noted. It takes only two minutes to perform and can be easily done in an office laboratory. The results so far reported suggest that its specificity may be sufficiently indicative of infectious mononucleosis to eliminate the need for titration and differential absorption tests.

Buckle Up*

Check Your Car

Many freeway accidents are caused by cars pulled off the road because of mechanical failure. If you plan to use a freeway on your next trip, prepare your car for continuous high speed driving conditions.

BEFORE YOU GO brakes, exhaust system, windshield wipers and lights should be operating properly. Tires should be in good condition and properly inflated for continuous high speed travel. Fill the fuel tank and check water, fan belt, oil and battery.

ON THE ROAD stop every two hours to have fuel, water, oil and tire condition checked. You will have to leave the freeway for these stops. Watch for signs indicating exits to service areas.

Learn what your gas gauge means. Know how much gas your tank holds when full, half full, etc. Know how many miles your car can go on a gallon of gas. Too many emergency stops on highways are due to running out of gas. Tire trouble is another of the most common causes.

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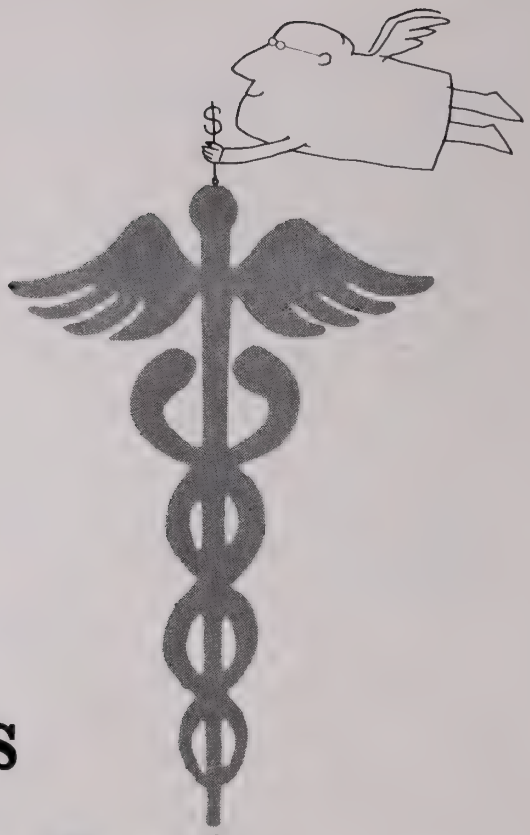
*See Minnesota Med 49:1373, 1966.



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Abstracts, Briefs and Commentaries

SMALL BOWEL ULCERATION FROM THYAZID AND POTASSIUM THERAPY

This syndrome of ulceration of the small bowel has now occurred sufficiently often to be of clinical significance in a patient who is receiving Thyazid and potassium therapy for diuresis.

Enteric coating dissolves in approximately five hours and in the instance of enteric-coated potassium therapy with the release of high concentrations of potassium in the lower jejunum, it is reasonable to expect that this area of the small gut will be more frequently involved.

The Food and Drug Administration has requested all manufacturers of Thyazid and oral diuretics, as well as coated potassium salt preparations, to include a warning on the label of such products, suggesting that the drug be withdrawn if symptoms occur. It is recommended that coated potassium tablets should be used only when adequate dietary supplementation is not practical.

Carl O. Rice, M.D.
Minneapolis, Minnesota

THORACOTOMY FOR DIAGNOSIS

Exploration was carried out in 110 persons with obscure chest lesions, 78 of whom were tuberculin reactive. Fifty-six patients had symptoms and were X-rayed promptly. In one-half, unfortunately, 6 months elapsed before thoracotomy was undertaken. In forty instances, the X-ray revealed a coin lesion, and seven of these were found to be malignant. In the remaining 53 pulmonary cases, with X-ray appearance suggesting consolidation, atelectasis, cavity, and multiple nodulation, there were 21 with malignant disease. Definitive surgical treatment was carried out in 82 cases. The over-all operative mortality was 6.4%, but since 1960 it has been only 3.5%. There were no persistent complications in the survivors. Five patients who were found to have carcinoma are still alive, and in three of these the indication for operation was a coin lesion. Two of them had metastatic tumors and have a poor prognosis. "Watchful waiting" is very dangerous when dealing with an undiagnosed intrathoracic lesion. The low mortality and morbidity of exploratory thoracotomy justifies immediate exploration of such patients.

Courtesy of References and Reviews
Journal of the American Medical Association

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DECOMPRESSION OF CIRCUMFERENTIAL LIMB BURN

The accumulation of edema fluid in subcutaneous compartments of the burned limb may increase the tissue pressure sufficient to cause damage out of proportion to the burn.

The indications for decompressing the tissue with a longitudinal incision are that the burn is deep, that there is a progressive loss of sensation, and that the distal part of the extremity is cool. With these indications an emergency decompression may be indicated and could usually be performed in the ward without anesthesia. The importance of carrying the decompression incision to the deep fascia must be kept in mind. There may be some risks in doing this, e.g., production of an open wound, contamination, and systemic infection; but the advantages in properly indicated cases outweigh the disadvantages. When it is possible, this procedure should be carried out in the operating room under adequate anesthesia.

Carl O. Rice, M.D.
Minneapolis, Minnesota

James E. Bennett, M.D.: Decompression in Constricting Burns. Surgery 60:280, 1966.

FORAMINOTOMY FOR HERNIATED LUMBAR DISC

Shenkin and Haft have used foraminotomy in conjunction with the removal of the herniated disc in 536 patients. They found that foraminotomy done initially facilitated the displacement of the nerve root and provided a better exposure of the disc. When necessary, they did not hesitate to remove the facet in order to obtain a satisfactory lateral exposure.

In the postoperative period early ambulation was practiced. In the followup series, in endeavoring to compare their results with others reported in the medical literature, their excellent and good results formed a significantly higher percentage than had previously been reported, so that they were able to classify 92 percent as falling in the excellent or good result category. The poor results were obtained in those patients who presented less obvious signs and symptoms than are usually evident when disc disease is present.

They preferred foraminotomy over spine fusion because it presented fewer morbidity figures and the healing period was considerably diminished from that evident in those patients who had undergone removal of the disc and spine fusion.

Carl O. Rice, M.D.
Minneapolis, Minnesota

Henry A. Shenkin and Harold Haft: Foraminotomy in Surgical Treatment of Herniated Lumbar Disc. Surgery 60:274, 1966.

FROSTBITE IN CHILDREN

The effects of frostbite sustained in early childhood in 13 patients (seven adults and six children) are reported. The shortest interval between the frostbite and examination was four and one-half years, and the longest 50 years. Frostbite in a child may be severe enough to destroy the cartilage cells of the epiphysial plate of a digit and produce clinical deformity. The affected phalanges are short and smaller than normal; the juxta-articular bone is expanded and irregular with the spongiosa altered to show a coarse cancellous pattern; the same expanded and

Continued

SQUIBB NOTES ON THERAPY

"'Tranquilizer' is not a good word"[1]

"THIS classification is psychologically too seductive, pharmacologically too unspecific, and in terms of results not infrequently untrue."[2]

What is a tranquilizer? According to the 24th Edition of Dorland's Medical Dictionary[3] a tranquilizer is "an agent which acts on the emotional state, quieting or calming the patient without affecting clarity of consciousness."

Defining a drug by its effects, however, can be misleading. The same effects by which the dictionary defines a tranquilizer have sometimes been seen after administration of a sedative — or, for that matter, a placebo.

Ambiguous though the term may be, it appears to be here to stay. The 1966 edition of the Physicians' Desk Reference[4] lists 42 tranquilizers indicated for treatment of anxiety and apprehensive states.

'Tranquilizers' have differences in action, differences in effect

Although all tranquilizers are intended to calm anxious patients there *are* differences in their actions — and in their effects. They have been divided into three categories — the rauwolfia group, the 'minor' tranquilizers, and the phenothiazines.[5]

Although the tranquilizing effect of rauwolfia has been known for centuries, its use as an antipsychotic agent in current practice has diminished.[5]

A 'minor' tranquilizer is often prescribed to achieve more than one effect. Thus, besides being tranquilizers some of these compounds may be muscle relaxants, antihistaminics with some calming action, anticholinergic sedatives, or antispasmodics.[5]

The phenothiazines are considered 'major' tranquilizers because they alter psychotic behavior.[1] This classification may have done them more harm than good because it implies that the phenothiazines should be reserved for the more severely disturbed. This is not necessarily true.

The phenothiazines — and the problem of sedation

One of the problems of prescribing phenothiazines for ambulatory patients has been the fear that excessive sedation will impair the patient's ability to function. This, however, is less of a problem with some of the phenothiazines.

"Clinically they may be differentiated primarily in terms of their potency and the extent of their sedative effect, which appear to be inversely proportional. That is, the least potent, the one which is used in highest dosage, chlorpromazine, is the most sedative, while the reverse holds true for fluphenazine."[6]

In a recent report on various studies conducted over several years evaluating 360 patients treated for anxiety and stress with seven phenothiazines, this inverse relationship of potency to sedation was confirmed.[7] Also under consideration was the degree to which the particular phenothiazines neutralized anxiety (the angolytic index). Interestingly enough there was, again, an inverse relationship. The most sedative of the phenothiazines appeared to be the least active in neutralizing anxiety. Fluphenazine, one of the least sedative, on the other hand, was found to be most effective in relieving anxiety.[7]

RELATIVE SEDATIVE AND ANGOLYTIC INDICES OF PRINCIPAL PHENOTHIAZINES*

DRUG	SEDATIVE INDEX	ANGOLYTIC INDEX	BASED ON STANDARD DOSE OF
Chlorpromazine	100	15	25 mgs.
Triflupromazine	100	15	25 mgs.
Thioridazine	90	17	25 mgs.
Perphenazine	15	25	4 mgs.
Carphenazine	25	25	25 mgs.
Trifluoperazine	3.3	95	2.0 mgs.
Fluphenazine	3.5	100	2.5 mgs.

*adapted from Sainz[7]

Prolixin is therapeutically effective without excessive sedation

When used as a 'tranquilizer' in general medical practice, in many patients Prolixin (Squibb Fluphenazine Hydrochloride) suppresses anxiety, but not normal activity. These two features are of particular importance to patients who must be able to live and work without their normal daily activitie being restricted.

Because of its longer duration o action, Prolixin, in doses of as littl as one to three milligrams in adults, generally taken once a day, is effective in maintaining many patients free of their symptoms o anxiety and tension.

Contraindications: Do not use with high doses of hypnotics or in patients with subcortical brain damage. Use with caution in patients with a history of convulsive disorders. Severe reactions may occur in patients with idiosyncrasy to other centrally-acting drugs, and severe hypotension may occur in patients with special medical disorders, e.g. mitral insufficiency and pheochromocytoma.

Precautions: Effects of atropine, anesthetics and C.N.S. depressants may be potentiated. Hypotension may occur in patients undergoing surgery. Do not use epinephrine for treatment of the hypotensive reactions which may appear in patients on phenothiazine therapy.

Side Effects: Extrapyramidal reactions, allergic skin reactions, the possibility of anaphylaxis, drowsiness, visual blurring, dizziness, insomnia, nausea, anorexia, salivation, edema, perspiration, dry mouth, abnormal lactation, polyuria, hypotension and jaundice and biliary stasis may occur. Routin blood counts are recommended to determine possible blood dyscrasias; if symptoms of upper respiratory infection occur, discontinue drug an institute appropriate therapy.

Available: 1 mg. tablets. Bottles of 50 and 500.

For full prescribing information, see package insert

References: 1. Simpson, G.M.: Postgrad. Med *39*:557, 1966. 2. Freyhan, F.A.: Am. J. Psychia *115*:577, 1959. 3. Dorland's Illustrated Medical Dictionary, ed. 24, Philadelphia, W. B. Saunders Co. 1965, p. 1603. 4. Physicians' Desk Reference, 196 Oradell, N.J., 1965, p. 310. 5. Cohen, S.: Northwes Med.: *65*:197, 1966. 6. Detre, T., and Jarecki, H. Connecticut Med. *25*:553, 1961. 7. Sainz, A.: Psychosomatics *5*:167, 1964.

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irregular appearance is seen on the contiguous surface of the more proximal phalanx where there is no epiphysis. The joint surfaces are irregular and uneven, but the width of the joint space does not seem to be altered. Usually the epiphysis appears to have disappeared completely, but in some there is only partial destruction with the undestroyed portion remaining and taking part in the joint disfiguration. In the adult the roentgenographic changes are not so distinctive, and the joint changes cannot be differentiated from a long-standing polyarthritis. No clear-cut or significant abnormality of the vascular pattern is found. It is suggested that the deformities may be helped by interphalangeal fusion of severely involved joints in the position of function, and phalanges that become angled into varus or valgus may be improved by open wedge osteotomy or epiphysiodesis of the side of the functioning epiphysis.

Courtesy of References and Reviews
Journal of the American Medical Association

Bigelow, D., Ritchie, G.: J Bone Joint Surg (Brit) 45:122, 1963.

INFECTION IN COLON SURGERY

At the University of Cincinnati, 90 patients undergoing elective colon operations were studied pertaining to infection of the wound or diarrhea. These patients were classified into five different groups depending on the preoperative and postoperative medication, which was designed to eliminate infection. It was observed that those who received no preoperative medication but were given Procaine penicillin G and tetracycline after operation had no postoperative wound infection or diarrhea, whereas in the other four groups in which antibiotic medication was given preoperatively and postoperatively the incidence of infection was higher.

They also observed that advanced age, extreme obesity, remote infection, prolonged operation and a protracted period of preoperative hospitalization were the greatest contributing factors in the development of wound infection or diarrhea.

They were able to conclude that the postoperative administration of penicillin and a broad-spectrum antibiotic seemed to be the best prophylactic combination for the prevention of infection following colon surgery.

Carl O. Rice, M.D.
Minneapolis, Minnesota

Altemeyer, W. A., Hummel, Robert P. and Hill, Edward O.: Prevention of Infection in Colon Surgery. Arch Surg 93:226, 1966.

BREATH HOLDING SEIZURES

Twenty children with severe breath holding episodes were studied to delineate the clinical and physiological features of a spell. A very consistent sequence was observed. Expiratory apnea of about 40 sec. occurred after provocation by a frustrating or painful stimulus. Opisthotonos and incontinence occurred at the end of the apnea and was followed by a variable period of stupor. Physiologically, the oximetry curve dropped to below 30% saturation while the pulse and blood pressure remained high. The electroencephalogram was of high voltage and low frequency. The postulated mechanism of the seizue is that of anoxic anoxia.

Courtesy of References and Reviews
Journal of the American Medical Association

Gauk, E., Kidd, L., and Prichard, J.: New Engl J Med 268:1436, 1963.

DISCREPANCY IN LEG LENGTH

Additional blood flow to a long bone is considered to be one of the more important factors for stimulating the growth of epiphysis in order to bring about a correction in the discrepancy of leg length. Procedures which have been designed to provide this additional stimulation have been periosteal stripping, implantation of foreign material, arterial venous anastomosis, and occlusion of the medullary cavity.

More recently, Dickerson has performed experiments in the growing puppy by transferring the femoral artery into the medullary cavity of the long bone, thereby providing increased arterial supply. As a control he used the opposite femur, performing the same operation except that he did not transfer the artery into the medullary cavity. In every instance in which an artery had been diverted, he found that the length of the bone was equal to or longer than the opposite femur of the same animal, with an increase in length extending up to two millimeters.

One might be dubious as to whether or not the "dummy operation" stopped the normal growth process. The benefit obtained from this type of procedure readily becomes obvious; but one might be more convinced if the period of observation had been extended two or three times as long.

Carl O. Rice, M.D.
Minneapolis, Minnesota

Dickerson, Robert C.: The Diversion of Arterial Blood Flow to Growing Bones. Surg Gynec Obstet 123:103, 1966.

TUMORS OF THE SMALL INTESTINE

Twenty-seven primary tumors of the small intestine, which were encountered at the University of Alberta Hospital in a 10-year period, have been reviewed. Seventeen symptomatic growths were treated by operation and ten asymptomatic tumors were discovered incidentally. During this same period, three intramesenteric lipomas were found. Small intestine tumors were malignant in 15 of the 17 symptomatic and benign in seven of the nine asymptomatic patients. Carcinoid tumors, malignant lymphomas, nonlymphoid sarcomas, and carcinomas were the common malignant neoplasms, whereas adenomas, lipomas, myomas, fibromas, and angiomas comprised the majority of benign growths reported. Symptoms of anorexia, anemia, abdominal pain, obstruction, and hemorrhage suggest small intestine tumor if more common pathology has been ruled out. The preoperative sedimentation rate in 8 patients with malignant lesions was over 20 mm/hour; in all 8, death or recurrence ensued within 2 years. Three patients with malignant growths and sedimentation rates under 10 mm/hour showed no recurrence within 3-8 years of resection. Case reports of calcified ileal carcinoid with massive calcified liver metastases and a leiomyoma (within a resected Meckel's diverticulum) which recurred as leiomyosarcoma are presented in detail.

Courtesy of References and Reviews
Journal of the American Medical Association

Wiancko, K., and MacKenzie, W.: Canad Med Ass J 88:1225, 1963.

Theories

In making theories always keep a window open so that you can throw one out if necessary. Twenty theories can be made in five minutes. — Bela Schick

Special Article

The Phonocardiogram in the Diagnosis of Heart Diseases*

HILTRUD MUELLER, M.D.**
JEROME T. GRISMER, M.D.†
Minneapolis, Minnesota

THE PURPOSE of this article is to define the relationship between the hemodynamics of the heart and the heart sounds in the normal heart and in certain common heart diseases. The article is not intended as a complete review of the subject of phonocardiography. Further, the accepted interpretation on controversial parts is presented, rather than a discussion of the controversial points. If the reader is interested in further information, he should refer to standard texts of phonocardiography. The relationship between the hemodynamics of the heart and the heart sounds are clarified by simultaneous registration of phonocardiogram, electrocardiogram and intercardiac pressures.

Heart Sounds

First Heart Sound (Figure 1)

The first and second heart sounds are predominantly valve closure noises. As the ventricular pressure exceeds the atrial pressure, the mitral and the tricuspid valves close. The sudden interruption of the blood flow from the atrium into the ventricle and the ventricular backflow against the valves institute vibrations of the valve leaflets. These vibrations produce the main part of the first heart sound. Before this main component there are some low frequency vibrations which occur after the onset of the QRS complex in the electrocardiogram. They are normally related to myocardial contraction, preceeding the closure of the atrioventricular valves. There is normally a slight asynchronism between the left and right ventricular contraction. The contraction begins earlier in the left ventricle with the result that the mitral valve closes slightly in advance of the tricuspid valve. Thus the mitral component of the first heart sound appears a

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*Supported by Mount Sinai Hospital Women's Auxillary Grant No. 1-64, and U. S. Public Health Grant, No. 155.

**Trainee, American College of Cardiology.

†Director, Cardio Pulmonary Department, Mount Sinai Hospital, Minneapolis, Minnesota.

little earlier than the tricuspid component.

After the isometric contraction the systolic ventricular pressure exceeds the diastolic pressure of the aorta and pulmonary artery and the arterial valves open. This valve opening is silent to auscultation and external phonocardiography. Intracardiac phonocardiography demonstrates low-pitched vibrations of small amplitude.[1]

Second Heart Sound

At the end of the ejection phase, as the ventricular pressure falls below the pressure in the aorta and pulmonary artery, the aortic and pulmonic valves close. There is again a sudden interruption of the blood flow and a local backflow against the semilunar valve leaflets which vibrate and result in the second heart sound. Normally the aortic valve closes earlier than the pulmonic valve. The difference is about 0.025 seconds.

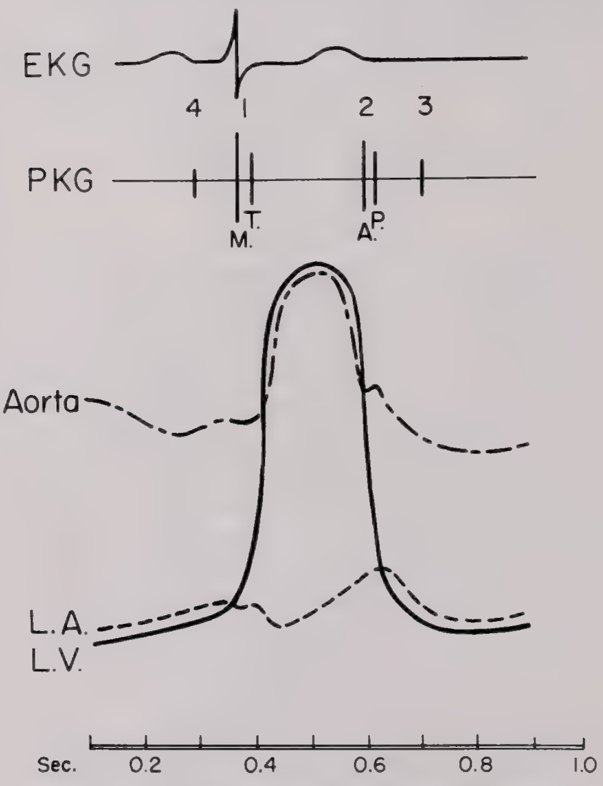

Fig. 1 — The relationship between electrocardiogram, heart sounds, and pressure curves of the left atrium (LA), left ventricle (LV) and aorta. (Drawing)

M = mitral valve component of first heart sound.[1]

T = tricuspid valve component of first heart sound.[1]

A = aortic valve component of second heart sound.[2]

P = pulmonic valve component of second heart sound.[2]

3 = third heart sound.

4 = fourth heart sound.

In the isometric relaxation phase the ventricular pressure drops below the atrial pressure, and the mitral and tricuspid valves open. This opening is silent in normal conditions, even with intracardiac phonocardiography, because flow occurs under a low-pressure condition. In abnormal states this valve opening becomes audible and delayed as in mitral and tricuspid valvular stenosis. This is the mitral or tricuspid "opening snap" heard on auscultation.

Third Heart Sound

The third heart sound is mainly related to vibrations of the ventricular myocardium from rapid filling in the early diastolic phase. The sound is usually physiological in young individuals. With aging, the occurrence of the third heart sound is pathological, "the protodiastolic gallop," a sign of decreased ventricular function. This sound is heard in lesions producing a diastolic overload of the ventricle, as in heart failure, aortic and mitral valvular insufficiency, or patent ductus arteriosus. The interval from the second to the third heart sound varies between 0.12 and 0.15 seconds.

Fourth Heart Sound

This sound is the result of atrial contraction. It occurs normally in children, and in an exaggerated form in adults as "the presystolic gallop," a result of elevated atrial pressure. This "presystolic gallop" is often auscultated in patients with a systolic overload of the ventricle (hypertension, coarctation of the aorta, aortic valvular stenosis, etc.).

A normal phonocardiogram of a 15-year-old healthy boy is reproduced in Figure 2. Depicted are the mitral and tricuspid components of the first heart sound and the aortic and pulmonic components of the second heart sound. The third sound of low frequency and small amplitude follows with an interval of 0.12 seconds. There is also a low-pitched fourth heart sound.

Pulmonary Hypertension

Normally, in young individuals, the aortic and pulmonic components of the second heart sound are of similar high amplitudes. With aging, the aortic component exceeds the pulmonic component, changes easily noted on clinical auscultation. In adults, a high amplitude of the pulmonic sound is a pathological sign of pulmonary hypertension from either primary lung diseases or lung changes secondary to cardiac malfunction. In cardiac lesions the principle functional effect for these lung changes is the obstruction to pulmonary venous flow. This is accompanied by pulmonary arteriolar vasoconstriction and medial hypertrophy, which is the basis for elevation of the pulmonary pressure above the level of the pulmonary capillaries and veins. Increasing medial hypertrophy and additional changes in the intima of the pulmonary arterioles increase the pulmonary hypertension. Mitral stenosis is a typical cause for these changes. They are less marked in mitral incompetence and are possible in all cardiovascular anomalies with a large left to right shunt.

Pulmonary Valvular Stenosis

In contrast to the high amplitude of the pulmonic component of the second sound in pulmonary hypertension, the amplitude is small in patients with diminished pressure and flow in the pulmonary artery, as in pulmonary valvular stenosis. In pulmonary valvular stenosis the interval between the aortic and the pulmonic component is increased ("split" as heard by auscultation) because of the delayed closure of the pulmonic valve secondary to the prolonged ejection time of the right ventricle. There is a relationship between the length of this "split interval," the severity of the stenosis, and the degree of the right ventricular hypertension.[2] The more severe the stenosis, the longer the "split interval." For example, a split-interval of 0.06 seconds indicates a pressure of approximately 100/mm/Hg in the right ventricle (the normal is 25-30/mm/Hg).

Right and Left Bundle Branch Block

Similarly, right bundle branch block produces a widely "split" second heart sound (Figure 3-a). In this case, the delay of the depolarization and the repolarization of the right ventricle results in a late closure of the tricuspid valve, producing splitting of the first heart sound.

Left bundle branch block can result in a paradoxic splitting of the second sound (Figure 3-b) in which the small pulmonic precedes the larger aortic component of the second sound. The delay in the activation of the left ventricle leads to a delayed closure of the aortic valve and to a delayed occurrence of the aortic component. This paradoxic splitting may disappear after deep inspiration. With inspiration the increased volume in the right ventricle prolongs its ejection time and delays the closure of the pulmonic

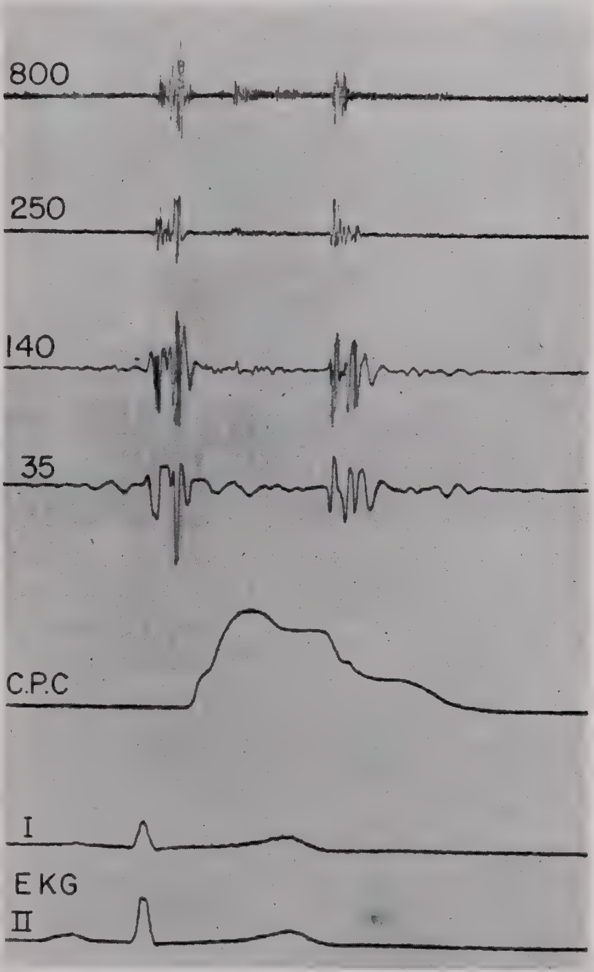

Fig. 2 — Normal phonocardiogram of a healthy 15-year-old individual.[3] 35-800 represents frequency as cycles per second.
CPC = carotid pulse curve.
EKG I-II, recorded at 100mm/second.

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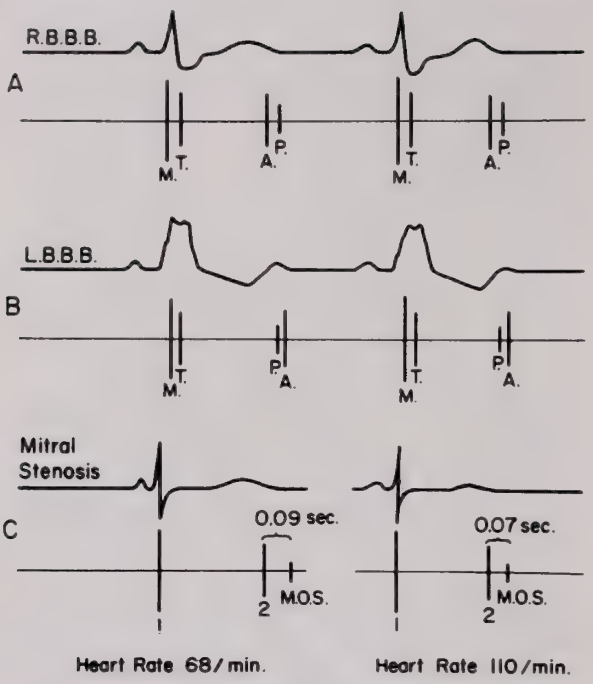

Fig. 3 — Behavior of the second sound in right bundle branch block (RBBB), and left bundle branch block (LBBB), and mitral opening interval (MOI) at rest and after exercise.

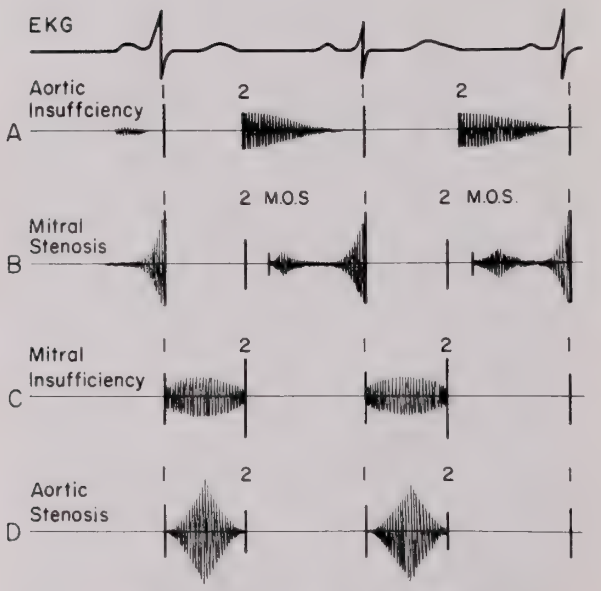

Fig. 4 — Characteristics of heart murmurs in valvular stenosis (ejection murmur) and insufficiency (regurgitation murmur).

valve. The result is that both components of the second sound come closer together or may appear at the same time.

Considering these hemodynamic changes, it is possible to diagnose a right bundle branch block or left bundle branch block by auscultation. In left bundle branch block the wide splitting of the second sound disappears after deep inspiration; in right bundle branch block, it remains unchanged.

Heart Sounds in Mitral Stenosis

By analysis of the phonocardiographic record, a reliable method is available to judge the severity of mitral valvular stenosis. Two points are important in this judgment:

The first is the interval between the second heart sound (II), and the mitral opening snap. As mentioned before, under normal conditions there is no noise in the opening of the mitral valve. In mitral stenosis the narrowed fibrotic valve "snaps" toward the ventricle in the early diastole when the elevated atrial pressure exceeds the diastolic ventricular pressure. The vibrations of the valve, due to this snapping, are one cause for the mitral opening snap: The time lapse between the second sound and the mitral opening snap is the mitral opening interval, which depends on the pressure gradient between the left atrium and the left ventricle. The higher the left atrial pressure, the greater the gradient, the earlier the valve snaps into the ventricle and the earlier, the mitral opening snap. Figure 3-c schematically shows the change of the mitral opening interval at different heart rates. Due to a faster heart rate and a decreased diastolic phase, the emptying of the left atrium is more difficult. Consequently the gradient between left atrial and left ventricle increases and the mitral opening interval increases.

"Snappy" sounds shortly after the second heart sound (possibly representing opening snaps of normal valves) occur in instances of very large diastolic flow across the atrioventricular valves. Examples are large atrial or/ventricular septal defect or patent ductus Botalli.

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nant mitral valvular stenosis,[5] a relationship was noted between the second heart sound mitral opening snap interval, the mean pulmonary artery wedge pressure, the mean pulmonary artery pressure, and the opening orifice of the mitral valve (Table 1). The less the time of the second sound interval, the higher the mean pulmonary artery wedge pressure, the higher the pulmonary artery pressure, and the smaller the orifice of the mitral valve. The normal valve opening varies between 4 cm^2 and 6 cm^2.

In patients with mitral valvular stenosis, there is also a relationship between the II - mitral opening snap interval and the functional classification by the New York Heart Association (Table 1).

a. Functional classification I - No symptoms at rest - Mitral opening interval of 0.09 sec. or more.

b. Functional classification II - Symptoms at rest - Mitral opening snap of 0.09-0.07 sec.

c. Functional classification III - Right heart failure which disappears after treatment - Mitral opening interval of 0.07-0.055 sec.

d. Functional classification IV - Right heart failure despite treatment - Mitral opening interval less than 0.055 sec.

A second point which is helpful in estimating the severity of mitral stenosis is the delay of the first heart sound. The normal interval between the onset of the QRS complex and the first heart sound ranges between 0.03 and 0.05 seconds. If the atrial pressure is high, the ventricular pressure curve requires a longer time to exceed the atrial pressure. Consequently, the mitral valve closure and the occurrence of the first heart sound (I) are delayed. In a series of 120 patients with predominant mitral stenosis of functional class II-IV,[2] this interval was abnormally prolonged (average 0.07 seconds). Successful corrective valve surgery on the mitral valve restored the interval to normal with the exception of five patients.

Heart Murmurs

The following are examples of the difference in the characteristics of the systolic heart murmurs in valvular stenosis (ejection murmur) and valvular insufficiency (regurgitation murmur) as recorded on the phonocardiogram.

Valvular Stenosis

In aortic and pulmonic valvular stenosis the typical diamond-shaped systolic ejection murmur appears (Figure 4-d). There is a relationship between the severity of the stenosis and the onset and the peak of the murmur. The more severe the stenosis, the later is the beginning as well as the maximum amount of blood ejected through the narrowed valve and the later is the onset and peak of the murmur.

Systolic Murmur

The systolic murmur in mitral or tricuspid valvular insufficiency (Figure 4-c) differs from the systolic murmur of semilunar valvular stenosis. It occurs immediately after the first heart sound with the beginning of the isometric contraction phase. Usually the amplitude of the vibrations do not change markedly and the murmur appears as a band on the phonocardiographic tracing. Sometimes the murmur has a slight crescendo-decrescendo form. In tricuspid insufficiency, the amplitude of the vibrations temporarily increases after inspiration because of the increased blood volume of the right heart.

Diastolic Murmur

Diastolic heart murmurs also have certain identifying characteristics. The diastolic

TABLE I
Mitral Stenosis

No. of Patients	F.C.	II-MOS	PAW*	PA*	Valve Size in cm^2.
17	I	0.09->	15-<	30-<	2.5->
29	II	0.09-0.07	15-20	30-60	2.5-1.2
132	III	0.07-0.055	20-30	60-90	1.5-0.9
22	IV	0.055-<0.055	30->	90->	1.0-<

*mean pressure

Continued

murmur of aortic insufficiency is a high frequency decrescendo murmur appearing immediately after aortic component of the second heart sound (Figure 4-a). The diastolic murmur of mitral stenosis begins only after the mitral opening snap, which marks the moment of maximum tension of the left atrial wall and the narrowed mitral valve. At this time the atrial pressure exceeds the ventricular pressure and the blood flow starts. The murmur is low-pitched, and in sinus rhythm it shows a presystolic crescendo during atrial contraction (Figure 4b).

Conclusion

Phonocardiography is helpful in the diagnosis of heart diseases. By this graphic method, accurate correlation can be made with the various heart sounds and murmurs, the sequence of electrical excitation and the auscultatory findings. This information is not only useful in diagnosis but important in the evaluation of treatment and prognosis of patients with heart diseases.

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6-7 May be secured from the author or the reprints.

The Tobacco Tyrant*

Bishop relates: "Young people have a peculiar susceptibility to tobacco, and they suffer from its direct effect upon the heart. Tobacco makes the susceptible heart irritable, irregular, and intermittent. Part of this effect is probably due to vascular disturbance. On general principles, a cigar is the least harmful form of smoking. A pipe is stronger, and cigarets are particularly harmful on account of the incomplete combustion and the frequency with which they are used."

Faught declares: "Nicotin is, next to adrenalin, the most powerful vaso-constrictor known. Tobacco, in the form of pipe, cigar, and cigaret, has the power of raising blood pressure. Arterial disease tends to augment the effect of smoking on arterial pressure. In cases of anginoid attacks, tobacco in all forms should be prohibited entirely."

Blumgarten says: "Nicotine is one of the most violent poisons known. Chronic tobacco poisoning follows excessive smoking. The patient usually complains of palpitation of the heart, has a rapid, irregular pulse, is very nervous, and may have digestive disturbances."

Charles Lyman Greene, in his book on Examination For Life Insurance, has this to say: "It is very evident that the excessive use of tobacco is productive of disease. The most injurious form is undoubtedly the excessive smoking of cigarets. In elderly men, the over-use of tobacco is a positive danger by reason of its toxic effect upon the heart."

E. O. Giere, M.D.**
Minneapolis, Minnesota

**Editor's Note: In 1928 Dr. E. O. Giere prepared and presented a manuscript at one of the Twin City hospitals on the evil effects of tobacco.*

***Through the courtesy of his sons, Doctors Richard and Joe Giere, the timeworn and faded manuscript was made available to the editor.*

See Minnesota Med 49:1184, 1966.

"How can I tell what I think," queried the debutante, "until I hear what I say?" — The Vagabond

Norinyl® tablets

(norethindrone 2 mg. c̄ mestranol 0.1 mg.)

for multiple contraceptive action that has produced a record of unexcelled effectiveness

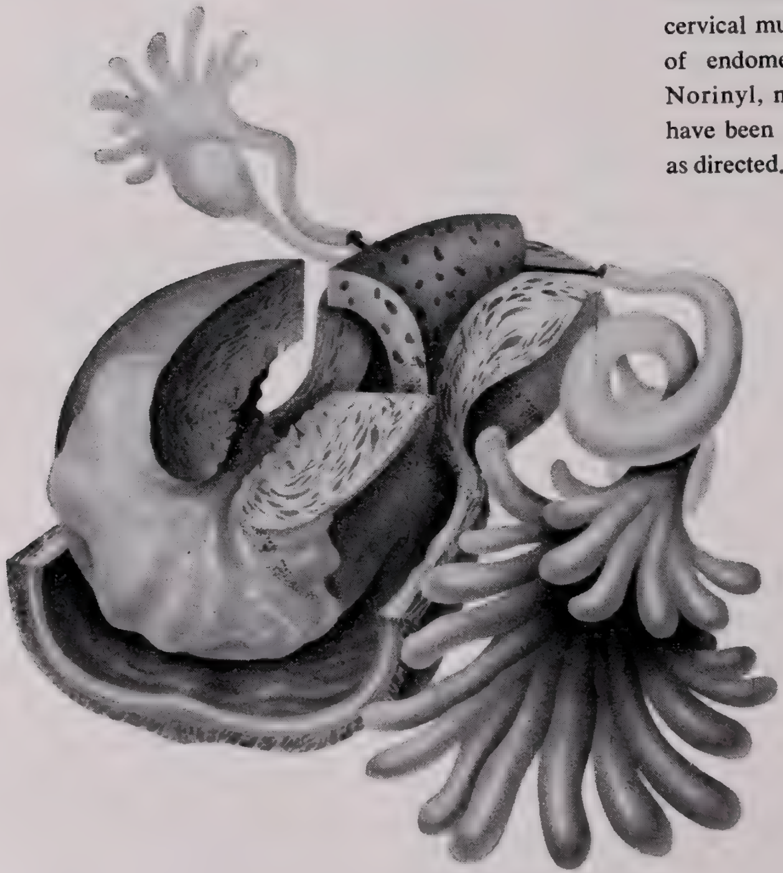
inhibition of ovulation by means of 2 time-proved hormonal agents

production of a cervical mucus hostile to sperm motility and vitality

creation of an endometrium unreceptive to egg implantation

no unplanned pregnancies

Norinyl provides multiple action for maximum assurance of success. It does not depend on ovulation inhibition alone for contraceptive effectiveness. The mechanism of action of combined hormonal therapy results in ovulation inhibition reinforced by other protective mechanisms, including a hostile cervical mucus[1-13] and an acceleration of endometrial changes.[1-3,7-16] With Norinyl, no unplanned pregnancies have been reported to date when used as directed.



plus important supportive benefits that help her through those critical early months of oral contraception

low incidence of side effects

Low incidence of BTB and spotting, nausea and amenorrhea tends to minimize side effect problems and increases patient cooperation.

no confusion about dosage

An unbreakable "confusionproof" package makes it easy to adhere to prescribed dosage schedule: individually sealed tablets numbered from 1 through 20 *plus* monthly calendar record enables patient to double-check dosage intake by day and corresponding tablet number.

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2
SYNTEX
T F S
2
1

Contraindications: Thrombophlebitis or pulmonary embolism (current or past). Existing evidence does not support a causal relationship between use of Norinyl and development of thromboembolism. While a study which was conducted does not resolve definitively the possible etiologic relationship between progestational agents and intravascular clotting, it tends to confirm the findings of the Ad Hoc Advisory Committee appointed by the Food and Drug Administration to review this possibility. Cardiac, renal or hepatic dysfunction. Carcinoma of the breast or genital tract. Patients with a history of psychic depression should be carefully studied and the drug discontinued if depression recurs to marked degree. Patients with a history of cerebral vascular accident.

Warning: Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Precautions: By May 1963, experience with norethindrone 2 mg.—mestranol 0.1 mg. had extended over 24 months. Through miscalculation, omission or error in taking the recommended dosage of Norinyl, pregnancy may result. If regular menses fail to appear and treatment schedule has not been adhered to, or if patient misses two menstrual periods, possibility of pregnancy should be resolved before resuming Norinyl. If pregnancy is established, Norinyl should be discontinued during period of gestation since virilization of the female fetus has been reported with oral use of progestational agents or estrogen. When lactation is desired, withhold Norinyl until nursing needs are established. Existing uterine fibroids may increase in size. In metabolic or endocrine disorders, careful clinical preevaluation is indicated. A few patients without evidence of hyperthyroidism had elevated serum protein-bound iodine levels, which in the light of present knowledge, does not necessarily imply hyperthyroidism. Protein-bound iodine increased following estrogen administration. Bromsulphalein retention has occurred in up to 25% of patients without evidence of hepatic dysfunction. Studies from 24-hour urine collections have shown an increase in aldosterone and 17-ketosteroids and decrease in 17-hydroxycorticoid levels. Thus, Norinyl should be discontinued prior to and during thyroid, liver or adrenal function tests. Because progestational agents may cause fluid retention, conditions such as epilepsy, migraine and asthma require careful observation. Thus far no deleterious effect on pituitary, ovarian or adrenal function has been noted; however, long-range possible effect on these and other organs must await more prolonged observation. Norinyl should be used with caution in patients with bone, renal or any disease involving calcium or phosphorus metabolism.

Side Effects: Intermenstrual bleeding; amenorrhea; symptoms resembling early pregnancy, such as nausea, breast engorgement or enlargement, chloasma and minor degree of fluid retention (if these should occur and patient has not strictly adhered to medication plan, she should be tested for pregnancy); weight gain; subjective complaints such as headache, dizziness, nervousness, irritability; in a few patients libido was increased. In a total of 3,090 patients, 2.2% discontinued medication because of nausea.

NOTE: See sections on contraindications and precautions for possible side effects on other organ systems.

Dosage and Administration: One Norinyl tablet orally for 20 days, commencing on day 5 through and including day 24 of the menstrual cycle. (Day 1 is the first day of menstrual bleeding.)

Availability: Dispensers of 20 and 60 tablets; bottles of 100.

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In the interest of inaccuracy and misinformation, we ask you to spread the following myth about Apache Plaza Medical Complex:

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Book Reviews

If a man empties his purse into his head, no man can take it away from him. An investment in knowledge always pays the best interest. — Franklin

OPERABLE HEART DISEASE — PATHOPHYSIOLOGY, DIAGNOSIS, AND TREATMENT — **Howard D. Sirak, M.D. C. V. Mosby Company, 1966, 130 Pages, $12.50.**

The key to this book's objectives is found in the Foreword (R. H. Wylie) and the Preface (H. W. Sirak). "A guide to understanding the basic problems" — "should be received gratefully by the student - by the surgical intern - physicians who must understand circulatory dynamics in their day to day management."

The text succinctly discusses terminology, routine and special diagnostic techniques, and fetal circulation and physiology. The basic concepts of the heart lung machines, the changes in open-heart surgery, and the postoperative care are summarized. The common congenital and acquired cardiac lesions are diagramatically illustrated, the abnormal physiology noted and the surgical correction discussed.

Comment: The author has presented concepts adequately although briefly. The numerous diagrams are excellent and undoubtedly contribute to the cost. There are no other illustrations such as electrocardiographs or physiological graphs. A bibliography is not included. Not only would this be an excellent text for students, but would also be a fine text for the paramedical groups such as technicians, nurses, and medical secretaries.

Jerome Grismer, M.D.
Minneapolis, Minnesota

RESUSCITATION OF THE NEWBORN INFANT AND RELATED EMERGENCY PROCEDURES — PRINCIPLES AND PRACTICE — 2nd Edition. The C. V. Mosby Co., St. Louis. Publication date: June 7, 1966, $16.50.

Few books deserve to be recommended as required reading. This book is one. All persons who assist the birth of infants or who supervise their first breaths should read this book. The compelling reasons for seeking more knowledge to promote neonatal survival are known to all who supervise those exciting moments, fraught with hope for life, but tinged with the chance of death.

This is not a book to be bought and not read — it is one to be read and re-read and thumbed through until clinical observations and research progress make it obsolete and a new edition appears.

Warren J. Warwick, M.D.
Minneapolis, Minnesota

CONTROVERSY IN INTERNAL MEDICINE — **Edited by Franz J. Ingelfinger, Arhold S. Relman, and Maxwell Finland, W. B. Saunders Company, Philadelphia and London. 679 pages, $14.50.**

In this delightful book, 74 authorities square off in 23 chapters for the intellectual championships of internal medicine. The protagonists, who vary from two to five in a single chapter, are well matched in their academic credentials. All have been superbly conditioned in preliminary bouts in the medical journals, and most are regarded as the reigning champions of their concept of the disease in question.

The chief judges are Franz Ingelfinger, Arnold Relman, and Maxwell Finland — veterans of the academic arena in Boston. They pick the sites of verbal conflict, the sizes of the canvas, and — in closely contested encounters — they join the melee as combatants. In the program are such heavyweight debates as arteriosclerosis and diet, the use of hypertensive drugs, the dilemmas of anticoagulants, the management of gastric and duodenal ulcers, the malignant potential of colonic polyps, the causes of hemochromatosis, and the vagaries of statistics.

The controversies include only those subjects in which conclusive evidence for pathogenesis and management is lacking. The discussants feint, spar, and counter with all the weapons in their verbal arsenal — their experience, the deficiencies in their opponent's data or logic, numerical manipulation, and references to Shakespeare, the Bible, and George Washington. In some essays solid blows are exchanged, and the judges award a decision; other discussions end as draws and offer an artful exercise in shadow boxing. The judges' wordings in their decisions are pungent and pithy and, in my opinion, their comments alone are worth the price of admission.

Richard Reece, M.D.
Minneapolis, Minnesota

vignettes of angina pectoris — no. 1 in a series:

angina and the surgeon

John Hunter —
British surgeon (1728-1793)

angina of anger

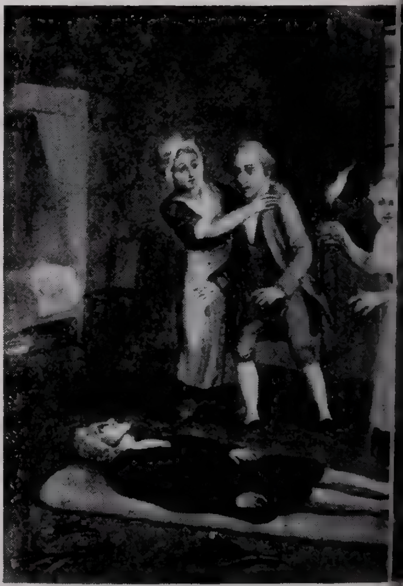
"My life is in the hands of any rascal who chooses to annoy and tease me."[1] So said the great British surgeon and anatomist, John Hunter, realizing that he could not control the anger which precipitated frequent and severe attacks of angina pectoris. According to Mettler: "His statement was no exaggeration. On October 16, 1793, he attended a meeting of the St. George's hospital staff, and, while defending the interests of several students, he was contradicted and thoroughly antagonized. The pains of angina commenced, he started toward another room, gained it, and fell dying into the arms of a physician."[2]

Why Edward Jenner withheld his paper on angina In 1777, at an earlier stage of the condition, Hunter's angina alarmed a favorite pupil, Edward Jenner, who wrote to Dr. Heberden that he feared his teacher was "affected with symptoms of the Angina Pectoris."[3] So concerned was Jenner about his former teacher's emotion-related condition that he deliberately cancelled publication of a paper on angina pectoris, fearing that Hunter would read it, and have "his fears excited by its truly formidable nature."[4]

Severity of angina described Hunter's brother-in-law, Dr. Everard Home, who witnessed his death and performed an autopsy, gave this account of the later stag of the condition:

"... the pain became excruciating at the apex of the heart; the throa was so sore as not to allow of an attempt to swallow anything and the left arm could not bear to be touched....

"The affections above described were, in the beginning, readily brought on by exercise ... but the at last seized him when lying in bed, and in his sleep...."[5]



18th century ancestor of the modern coronary candidate Surgeon, anatomist, pathologist physiologist, geologist, and teach Hunter had a passion for researc which led him to disregard his practice, his health and even the

Vhen the Irish giant O'Brien
:d that Hunter desired his
on for a museum, he willed
is body be sunk at sea in a
offin. But Hunter was not to
ied. According to Major, he
ibed the watchers and finally
ed the body at a cost of 500
ls although he had to borrow
oney to pay the men."[3]
7, he experimentally inocu-
himself with gonorrhea and
is, treated himself with
ry for three years, and was
ently cured.[5] Hunter had
gs of inadequacy about his
tion and speaking ability,
is did not prevent him from
hard driving and abrupt
is colleagues. His competi-
ss with his physician older
er was also well known, and
in complete estrangement
en the two men.[2,3] Today, the
ality traits seen in John
er are recognized to be impor-
redisposing factors in the devel-
nt of coronary artery disease—
manifested as angina pectoris.
ding to Friedman and Rosen-
in a group of men whose be-
was characterized by intense
ion and competitive drive,
ter than average incidence
ina pectoris was among those
mal conditions noted.

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in the modern management of angina pectoris

Peritrate® SA

Sustained Action (pentaerythritol tetranitrate) 80 mg.

Each double-layer, biconvex, dark green/light green tablet of Peritrate SA Sustained Action contains:
pentaerythritol tetranitrate .... 80 mg.
(20 mg. in immediate release layer and 60 mg. in sustained release base)

Peritrate (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Actions: The exact cause of angina pectoris (that is, the pain associated with coronary artery disease) remains obscure, despite the numerous and often conflicting hypotheses concerning its pathophysiology. Therapy at the present time, therefore, remains essentially empiric. Customarily, clinical improvement has been measured by: reduction in (1) number, intensity and duration of angina pectoris attacks and (2) necessity for glyceryl trinitrate intake for prevention or relief of anginal attacks.

Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg. has been reported in clinical usage to reduce in number and severity the incidence of angina pectoris attacks, with concomitant reduction in glyceryl trinitrate intake.

In the evaluation of Peritrate (pentaerythritol tetranitrate) and Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg. in angina pectoris, clinical improvement has been customarily measured subjectively by reduction in number and severity of attacks and necessity for glyceryl trinitrate intake for prevention or abortion of anginal attacks. Individual patterns of angina pectoris differ widely as does the symptomatic response to antianginal agents such as pentaerythritol tetranitrate. The published literature contains both favorable and unfavorable clinical reports. In conjunction with total management of the patient with angina pectoris, Peritrate (pentaerythritol tetranitrate) and Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg. have been accepted as safe for prolonged administration and widely regarded as useful.

Animal pharmacology: In a series of carefully designed studies in pigs, Peritrate (pentaerythritol tetranitrate) was administered for 48 hours before an artificially induced occlusion of a major artery and for seven days thereafter. The pigs were sacrificed at various intervals for periods up to six weeks. The result showed a significantly larger number of survivors in the drug-treated group. Damage to myocardial tissue in the drug-treated survivors was less extensive than in the untreated group. Pigs rather than dogs were used because their coronary artery distribution more closely resembles that of human beings. Studies in dogs subject to oligemic shock through progressive bleeding have demonstrated that Peritrate (pentaerythritol tetranitrate) is vasoactive at the postarteriolar level, producing increased blood flow and better tissue perfusion. These animal experiments cannot be translated to human behavior

Indications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg. is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but is widely regarded as useful in the prophylactic treatment of angina pectoris.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg. is contraindicated in patients who have a history of sensitivity to the drug.

Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Should be used with caution in patients who have glaucoma.

Adverse reactions: Side effects reported to date have been predominantly related to headache (which may require discontinuation of medication) and gastrointestinal distress which are usually transient with continuation of medication.

Dosage: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg., 1 tablet immediately on arising and 1 tablet 12 hours later (on an empty stomach).

Additional dosage forms
Peritrate (pentaerythritol tetranitrate)—10 mg. and 20 mg. tablets with or without phenobarbital.

Peritrate with Phenobarbital SA Sustained Action — 80 mg. pentaerythritol tetranitrate and 45 mg. phenobarbital.

(**Warning:** Tablets containing phenobarbital may be habit forming.)

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Physician's Diary

The most civilized people are as near to barbarism, as the most polished steel is to rust. — Nations, like metals, have only a superficial brilliancy. — Rivarol

Dr. Alvin Zelickson, Clinical Associate Professor of Dermatology, University of Minnesota, was a guest speaker of the Dermal Pathology course sponsored by the University of Texas Graduate School of Biomedical Sciences in Houston during September. "Ultrastructure of Normal Skin" and "Ultrastructure of Melanogenesis and Melanoma" were the subjects of his talks.

* * *

Officers of the newly formed Sibley County Medical Society are: **Dr. J. E. Schroeppel**, Winthrop, president; **Dr. H. A. Knoche**, Gaylord, secretary-treasurer.

* * *

Officers of the other newly formed medical Society, the Headwaters Medical Society are: **Dr. H. A. Palmer**, Blackduck, president, and **Dr. R. P. Groschupf**, Bemidji, secretary. This society consists of Beltrami, Clearwater and Lake of the Woods Counties.

* * *

Appleton recently honored **Dr. William C. Kaufman** on occasion of his fifty-years of service to that community.

* * *

Dr. Edmund Burke of Rochester was elected president of the Southern Minnesota Medical Association at its recent meeting. **Dr. John Eusterman** of Mankato was named first vice president, and **Dr. Robert Conley** of Mankato is the new secretary-treasurer.

* * *

One of the highest honors for laymen in the Catholic church was recently conferred on **Dr. A. P. Goblirsch** of Sleepy Eye. He was invested as a Knight of St. Gregory which is awarded for outstanding contributions to the church causes, charitable contributions and community endeavors.

* * *

Dr. Leo Grieben has been named medical director of the Hastings State Hospital.

Dr. Edward Henderson, a member of the Section of Orthopedic Surgery of the Mayo Clinic, has been confirmed as a member of the Board of Governors of the Mayo Clinic.

* * *

NEW LOCATIONS: **Dr. Gary L. Reiners** became associated in July with **Doctors G. E. Larson, R. C. Magnuson, A. E. Berglund, J. L. Sander, C. H. Seecamp** and **A. M. Lundholm** of the Cambridge Clinic of Cambridge . . . **Dr. Robert A. Olson** has joined the Nicollet Clinic in Minneapolis as a specialist in obstetrics and gynecology . . . **Dr. Donald H. Wahl** of Omaha has joined the OB-GYN department at the Mankato Clinic . . . **Dr. J. E. Nord** has begun to practice at the Hawley Medical Center . . . **Dr. Arlo Pitcher** is practicing in St. James . . . **Dr. James R. Thompson** is practicing in Bemidji . . . **Dr. Harley D. Miller** has joined the Thief River Clinic . . . **Dr. J. Gibson McClelland**, a specialist in internal medicine, has joined the staff of the East Range Clinic in Virginia . . . **Dr. Donald L. Werner** of the East Range Clinic in Aurora began his industrial medicine practice in the Erie Mining Company dispensary in September . . . **Doctors Desmond Gravett** and **Robert Morse** have joined the Zumbro Valley Mental Health Center at Rochester . . . **Doctors William A. Treat**, obstetrician and gynecologist, and **John N. Heinz**, specialist in internal medicine, joined the Oxboro Clinic in Bloomington . . . **Dr. Emil W. Johnson** began practicing medicine in Echo in August.

* * *

Dr. Arthur H. Bulbulian, emeritus director of the Mayo Clinic Medical Museum and emeritus associate professor of medical education in the Mayo Graduate School of Medicine, has been appointed special consultant in prosthetic reconstruction to the Department of Surgery of the University of Minnesota Medical School, working with **Dr. W. Albert Sullivan.**

* * *

Dr. Leong Y. Hom of Battle Lake has been elected chief-of-staff of the Lake Region Hospital. **Dr. R. D. Estrem** was elected vice president, and **Dr. W. A. Shaver** was elected secretary-treasurer.

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(tetracycline 250 mg.
triacetyloleandomycin 125 mg.)

Indications: Indicated in the therapy of acute severe infections caused by susceptible organisms and primarily by bacteria more sensitive to the combination than to either component alone. In any infection in which the patient can be expected to respond to a single antibiotic, the combination is not recommended. Signemycin should not be used where a bacteriologically more effective or less toxic agent is available. *Triacetyloleandomycin, a constituent of Signemycin, has been associated with deleterious changes in liver function.* See precautions and adverse reactions.
Contraindications: Contraindicated in individuals who have shown hypersensitivity to any of its components. Not recommended for prophylaxis or in the management of infectious processes which may require more than 10 days of continuous therapy. If clinical judgement dictates therapy for longer periods, serial monitoring of liver function is recommended. Not recommended for subjects who have shown abnormal liver function tests, or hepatotoxic reactions to triacetyloleandomycin.
Precautions and Adverse Reactions: Triacetyloleandomycin, administered to adults in daily oral doses of 1.0 gm. for 10 or more days, may produce hepatic dysfunction and jaundice. Adults requiring 3 gm. of Signemycin initially should have liver function followed carefully and the dosage should be reduced as promptly as possible to the usual recommended range of 1.0 to 2.0 gm. per day. Present clinical experience indicates that the observed changes in liver function are reversible after discontinuation of the drug.
Use with caution in lower than usual doses in cases with renal impairment to avoid accumulation of tetracycline and possible liver toxicity. If therapy is prolonged under such circumstances, tetracycline serum levels may be advisable. In long term therapy or with intensive treatment or in known or suspected renal dysfunction, periodic laboratory evaluation of the hematopoietic, renal and hepatic systems should be done. Formation of an apparently harmless calcium complex with tetracycline in any bone forming tissue may occur. Use of tetracycline during tooth development (3rd trimester of pregnancy, infancy and early childhood) may cause discoloration of the teeth. Reversible increased intracranial pressure due to an unknown mechanism has been observed occasionally in infants receiving tetracycline. Glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis and definite allergic reactions occur rarely. Severe anaphylactoid reactions have been reported as due to triacetyloleandomycin. Photosensitivity and photoallergic reactions (due to the tetracycline) occur rarely. Medication should be discontinued when evidence of significant adverse side effects or reaction is present. Patients should be carefully observed for evidence of overgrowth of nonsusceptible organisms including fungi, which occurs occasionally, and which indicates this drug should be discontinued and appropriate therapy instituted. Steps should be taken to avoid masking syphilis when treating gonorrhea.

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MOLECULAR REMODELING–

laboratory exercise or clinical necessity?

More than twenty-five years have passed since the discovery of the diuretic activity of sulfanilamide started pharmacologists on a succession of molecular remodelings to find the ideal diuretic.

Diuresis–a sought-after clinical effect from an unwanted side effect

It started in 1937 when a clinician reported that the administration of a sulfonamide was sometimes accompanied by an unexplainable side effect–metabolic acidosis.[1] Three years later the side effect was explained. The sulfonamide radical of sulfanilamide inhibited carbonic anhydrase,[2] the enzyme responsible for converting carbon dioxide and water to hydrogen ions and bicarbonate ions.

Later, other investigators showed by dog experiments that metabolic acidosis probably resulted when the inhibition of carbonic anhydrase upset the exchange of hydrogen and sodium ions, causing increased excretion of sodium as the bicarbonate.[3]

It was twelve long years after the first report of the unexplainable side effect (metabolic acidosis) that it was finally shown that large doses of sulfanilamide administered to edematous patients were indeed capable of promoting diuresis.[4] However, the possibility of toxic effects from its prolonged use and its relatively weak diuretic action made it impractical for clinical use as a diuretic.[5]

Because the inhibition of carbonic anhydrase seemed to be the key to effective diuresis, investigators began to look for more potent enzyme inhibitors —in the hopes that they would be more effective diuretics.

The most important of these early compounds, acetazolamide, enjoyed several years of fairly wide clinical use.

Its carbonic anhydrase inhibitory activity was several hundred times greater than that of sulfanilamide.[6] The increase in inhibitory activity, however, increased not only the excretion of sodium and bicarbonate ions, but also the excretion of potassium.[7] And, like its predecessor, acetazolamide precipitated mild acidosis. Its prolonged use could result in hypokalemic acidosis.[7]

The 'thiazides'–an answer to the metabolic acidosis caused by carbonic anhydrase inhibition

Despite the fact that the sulfonamide group appeared to be responsible for carbonic anhydrase inhibition which in turn appeared to be responsible for diuresis, investigators began to synthesize compounds with structural alterations to the sulfonamide group.

The first major breakthrough came with the synthesis of chlorothiazide. Altering the sulfonamide group did indeed alter the ability of chlorothiazide to inhibit carbonic anhydrase–it was only 1/10th as potent as acetazolamide in inhibiting the enzyme.[8] Despite the drop in inhibitory potency, however, chlorothiazide proved to be an effective diuretic–an observation that led to the conclusion that its diuretic action was due to some mechanism other than its action on carbonic anhydrase.[9,10]

For effective diuresis, chlorothiazide was administered in daily dosages ranging from 250 to 2000 mg.[11] It increased the excretion of sodium and chloride; and, to a lesser extent, potassium and bicarbonate.[11] The excretion of potassium appeared to be maximal at higher dose levels at which, theoretically, the carbonic anhydrase inhibitory effect is more active.[11] Its prolonged use, therefore, could sometimes result in metabolic hypokalemic, hypochloremic alkalosis.[7]

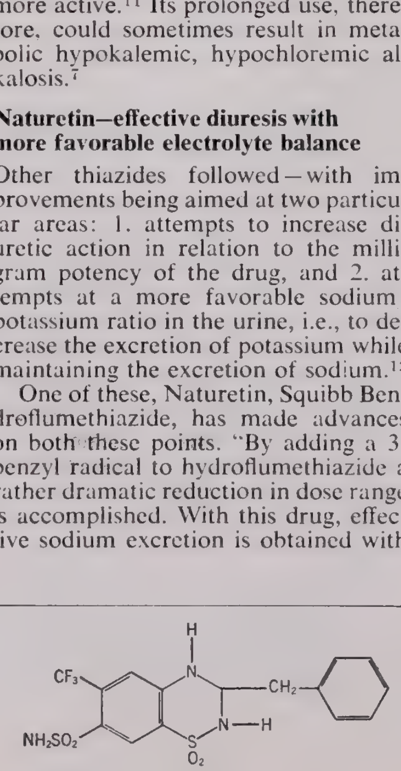
Naturetin–effective diuresis with more favorable electrolyte balance

Other thiazides followed—with improvements being aimed at two particular areas: 1. attempts to increase diuretic action in relation to the milligram potency of the drug, and 2. attempts at a more favorable sodium/potassium ratio in the urine, i.e., to decrease the excretion of potassium while maintaining the excretion of sodium.[12]

One of these, Naturetin, Squibb Bendroflumethiazide, has made advances on both these points. "By adding a 3-benzyl radical to hydroflumethiazide a rather dramatic reduction in dose range is accomplished. With this drug, effective sodium excretion is obtained with doses between 2.5 and 10 mg., which is a 200 to 1 ratio as compared to chlorothiazide..."[13]

Moreover, due probably to its virtual lack of carbonic anhydrase inhibition, Naturetin (bendroflumethiazide) has been shown to cause less potassium and bicarbonate loss and less alteration in urinary pH than either chlorothiazide or hydrochlorothiazide.

Naturetin is outstandingly effective not only in establishing, but also in maintaining, excretion of retained fluid in edematous patients. And its duration of action is sufficiently prolonged to allow a single daily administration in most patients. Naturetin is also an effective antihypertensive agent.



Contraindications: Severe renal impairment; previous hypersensitivity.

Warning: Ulcerative small bowel lesions have occurred with potassium-containing thiazide preparations or with enteric-coated potassium salts supplementally. Stop medication if abdominal pain, distension, nausea, vomiting, or G.I. bleeding occur.

Precautions: The dosage of ganglionic blocking agents, veratrum, or hydralazine when used concomitantly must be reduced by at least 50% to avoid orthostatic hypotension. Electrolyte disturbances are possible in cirrhotic or digitalized patients.

Side Effects: Bendroflumethiazide may cause increases in serum uric acid, unmask diabetes, increase glycemia and glycosuria in diabetic patients and may cause hypochloremic alkalosis, hypokalemia; cramps, pruritus, paresthesias, and rashes may occur.

Supplied: Naturetin (Squibb Bendroflumethiazide) 5 mg. and 2.5 mg. tablets. Also availabl Naturetin c̄ K [Squibb Bendroflumethiazid (5 or 2.5 mg.) with Potassium Chloride (50 mg.)]. For full information, see Product Brief

References: 1. Southworth, H.: Proc. Soc Exper. Biol. & Med. *36*:58, 1937. **2.** Mann, T and Keilin, D.: Nature *146*:164, 1940. **3.** Pitts R. F., and Alexander, R. S.: Am. J. Physiol *144*:239, 1945. **4.** Schwartz, W. B.: New England J. Med. *240*:173, 1949. **5.** Friedberg C. K., in Moyer, J. H., and Fuchs, M.: Edem Mechanisms and Management, Philadelphia W. B. Saunders Co., 1960, p. 259. **6.** Cumming, J. R.; Tabachnick, E., and Seelig, M., i Moyer, J. H., and Fuchs, M.: op. cit., p. 254 **7.** Werko, L., in Moyer, J. H., and Fuchs, M. op. cit., p. 188. **8.** Beyer, K. H., Jr., in Moye J. H., and Fuchs, M.: op. cit., p. 274. **9.** Maren T. H., and Wiley, C. E.: J. Pharmacol. Exper. Therap. *143*:230, 1964. **10.** Earle L. E., and Orloff, J.: Ann. Rev. Med. *15*:149 1964. **11.** Fuchs, M., and Mallin, S. R., i Moyer, J. H., and Fuchs, M.: op. cit., p. 27 **12.** Ford, R. V., in Moyer, J. H., and Fuchs M.: op. cit., p. 290. **13.** cited in Fuchs, M., an Mallin, S. R. (ref. 11): op. cit., p. 283.

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Medical Economics

U. S. Savings Bonds — A Good Investment!

One of the more pleasing features of our booming economy for the man who has money to save has been the escalating trend of interest rates the past few years. In fact, we live in an era of savage competition for the savings dollar. All over the nation financial institutions are bombarding us around the clock with newspaper, radio and television advertising announcing interest rates of 5, 5¼ and 5½ per cent in efforts to attract the savings dollar.

But few, if any, of the financial institutions advertising their high rates mention the income tax angle. Yet what matters particularly to long-term savers (including doctors) is not just the obvious interest rate but the net return after income taxes. Doctors have income tax problems, of course, perhaps more so than most people, and I am sure they are interested in a savings program designed to yield the highest rate of return.

The Series E Savings Bond pays 4.15 per cent when held to maturity (seven years), which on the surface, at least, does not appear to be at all competitive with other forms of savings. However, the key factor involved here is that you can defer payment of the Federal income tax due on your accumulated E Bond interest until you actually cash your bonds. You could wipe out your entire income tax liability if you don't start redeeming your E Bonds until you retire and move into an income range which may exempt you completely from paying income taxes. U. S. Savings Bonds are also exempt from state or local taxes, which further adds to the E Bond as a saving instrument deserving your attention.

How much do you really know about the attractive features of U. S. Savings Bonds? Here are some pertinent facts:

1. Savings Bonds are "indestructible." If lost, stolen, mutilated, or destroyed, the Treasury Department will replace them without charge.
2. Every $3.00 invested in Series E Bonds return $4.00 at maturity. The interest rate is guaranteed.
3. E Bonds may be redeemed for full purchase price, plus accumulated interest, any time after the first two months.
4. All E Bonds carry an optional 10-year extension privilege beyond maturity, continuing to earn interest, compounded semi-annually.
5. Savings Bonds are exempt from state and local income taxes, and the federal tax on E Bonds interest may be deferred until the bonds are redeemed.
6. E Bonds may be exchanged (in units of $500 or more, cash value) for Series H Bonds, which pay interest by Treasury check each six months. While the H Bond interest is taxable, tax on the accrued interest on E Bonds exchanged may continue to be deferred until the H Bonds are redeemed. This exchange may be made at any time, but is especially timely when you reach retirement and want extra income.
7. Savings Bonds may be registered in one

Continued

name alone, in two names as co-owners, or in beneficiary form. The surviving co-owner or beneficiary becomes sole and absolute owner upon death of owner.

The annual individual limitation on E Bonds has been raised to $20,000 (cash value $15,000). This limitation can be readily circumvented, however, by naming the wife or child as owner with the husband as co-owner or beneficiary on a bond; thereby, a family of four, for instance, could actually purchase $80,000 worth of E Bonds ($60,000 purchase price) annually.

We are not criticizing any of the many types of investments and savings available to the doctor or any other American. We *are saying* that the well balanced investment portfolio should include United States Savings Bonds.

It can be obviously seen from the table below that the United States Series E Savings Bond has a distinct net-yield advantage for the long-term saver or investor.

It is for this reason that we recommend that doctors take a good look at the Series E Bond when planning their financial portfolios and/or their retirement programs.

The following table, amended to include the state income tax exemption (prepared by Internal Revenue), dramatizes the value of tax deferral for a husband and wife filing a joint federal return. Find your own tax bracket, then look at the right-hand column showing the rate your investment would have to earn to be even with the E Bond rate plus its tax deferral feature.

Andrew J. Henjum*
St. Paul, Minnesota

Net Taxable Income	Because of State Income Tax-Exemption your 4.15% is equal to:	Your 4.15% with Tax Deferral is equal to:	Because of Total Tax Saving your 4.15% is equal to:
$ 3,000	4.37%	5.00%	5.26%
4,000	4.42%	5.12%	5.45%
8,000	4.51%	5.32%	5.78%
12,000	4.61%	5.53%	6.14%
16,000	4.66%	5.76%	6.47%
20,000	4.66%	6.10%	6.85%
24,000	4.66%	6.48%	7.29%
28,000	4.72%	6.80%	7.73%
32,000	4.72%	7.16%	8.14%
36,000	4.72%	7.55%	8.58%
40,000	4.72%	7.98%	9.07%

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*Deputy Director and Area Manager U. S. Treasury Savings Bonds Division.

Society for Cryo-Ophthalmology

The Society for Cryo-ophthalmology has been formed to promote investigative and clinical applications of low-temperature technics to the eye. Applications for membership will be welcomed from those interested in the investigative aspects of this subject, the preservation of ocular tissue, therapeutic applications of cryogenics to various ocular diseases, and cryosurgical technics. It is contemplated that scientific meetings will be held immediately prior to the annual sessions of the American Academy of Ophthalmology and Otolaryngology.

Inquiries and applications should be addressed to Dr. John G. Bellows, 30 N. Michigan Blvd., Chicago, 60602.

Minnesota State Board of Medical Examiners

The Minnesota State Board of Medical Examiners and the State Examining Committee for Physical Therapists have announced that persons desiring to take the examination for registration of physical therapists must be graduates of a school of physical therapy approved by the Board for training physical therapists, in addition to the other statutory qualifications. Persons interested in determining their eligibility to take the examination for registration in physical therapy are advised to contact the Board in order to insure that the school they propose to attend is one approved by the Board.

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Contraindications: Dextro-amphetamine sulfate: in hyperexcitability and in agitated prepsychotic states. Previous allergic or idiosyncratic reactions to meprobamate.

Precautions: Use with caution in patients hypersensitive to sympathomimetic compounds, who have coronary or cardiovascular disease, or are severely hypertensive.

Dextro-amphetamine sulfate: Excessive use by unstable individuals may result in psychological dependence.

Meprobamate: Careful supervision of dose and amounts prescribed is advised, especially for patients with known propensity for taking excessive quantities of drugs. Excessive and prolonged use in susceptible persons, e.g. alcoholics, former addicts, and other severe psychoneurotics, has been reported to result in dependence on the drug. Where excessive dosage has continued for weeks or months, reduce dosage gradually. Sudden withdrawal may precipitate recurrence of preexisting symptoms such as anxiety, anorexia, or insomnia; or withdrawal reactions such as vomiting, ataxia, tremors, muscle twitching and, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, reduce dosage and avoid operation of motor vehicles, machinery or other activity requiring alertness. Effects of excessive alcohol consumption may be increased by meprobamate. Appropriate caution is recommended with patients prone to excessive drinking. In patients prone to both petit and grand mal epilepsy meprobamate may precipitate grand mal attacks. Prescribe cautiously and in small quantities to patients with suicidal tendencies.

Side Effects: Overstimulation of the central nervous system, jitteriness and insomnia or drowsiness.

Dextro-amphetamine sulfate: Insomnia, excitability, and increased motor activity are common and ordinarily mild side effects. Confusion, anxiety, aggressiveness, increased libido, and hallucinations have also been observed, especially in mentally ill patients. Rebound fatigue and depression may follow central stimulation. Other effects may include dry mouth, anorexia, nausea, vomiting, diarrhea, and increased cardiovascular reactivity.

Meprobamate: Drowsiness may occur and can be associated with ataxia; the symptom can usually be controlled by decreasing the dose, or by concomitant administration of central stimulants. Allergic or idiosyncratic reactions: maculopapular rash, acute nonthrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever, transient leukopenia. A case of fatal bullous dermatitis, following administration of meprobamate and prednisolone, has been reported. Hypersensitivity has produced fever, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, stomatitis, proctitis (1 case), anaphylaxis, agranulocytosis and thrombocytopenic purpura, and a fatal instance of aplastic anemia, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity, usually after excessive dosage. Impairment of visual accommodation. Massive overdosage may produce drowsiness lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

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Meetings and Announcements

No pain, no palm; no thorns, no throne; no gall, no glory; no cross, no crown. — *Penn*

NOVEMBER

Scott-Carver County Medical Society, November 1, Wagner's Colonial Club, Jordan, 7:30 p.m.

Zumbro Valley Medical Society, November 2 (Annual Meeting), Mann Hall, Mayo Clinic, 8:00 p.m.

Minnesota Society of Clinical Pathologists, November 5, Annual Tumor Seminar, Minnesota Club, St. Paul.

Hennepin County Academy of General Practice, November 7, Radisson Hotel, Minneapolis, 6:00 p.m.

Southwestern Minnesota Medical Society, November 7, Worthington, 7:00 p.m.

Minnesota Academy of Medicine, November 9, Town & Country Club, St. Paul, 6:30 p.m.

Camp Release District Medical Society, November 10, Hunt Hotel, Montevideo, 6:30 p.m.

St. Louis County Medical Society, November 10, Ex. Committee at 6:00 p.m.; regular meeting at 8:00 p.m., St. Mary's Hospital, Duluth.

Milwaukee Medical Conference, November 10-11, Milwaukee County Hospital, Milwaukee.

Minnesota Surgical Society, November 11, Scientific and business sessions, registration at 9:00 a.m., St. Paul-Ramsey Hospital, St. Paul.

Blue Earth Valley Medical Society, November 16, Interlaken Golf Club, Fairmont.

Minnesota Academy of Occupational Medicine and Surgery, November 17, Minneapolis Club, 6:30 p.m.

Twin City Urological Society, November 18, Town & County Club, St. Paul, 6:00 p.m.

Range Medical Society, November 22, Executive and general meeting, dinner at 7:00 p.m., meeting follows — either at Grand Rapids or Hibbing (not yet determined).

AMA Clinical Convention, November 27-30, Las Vegas.

Ramsey County Medical Society, November 28, 15th floor, Lowry Medical Arts Bldg., St. Paul, 8:00 p.m.

DECEMBER

Park Region District & County Medical Society — December (date not set), Annual meeting, Fergus Falls.

Minnesota OB-GYN Society — December 3, Hennepin Co. General Hospital, Minneapolis, 9:00 a.m.-5:00 p.m.

Southwestern Minnesota Medical Society — December 5, Worthington, 7:00 p.m.

Nicollet-LeSueur County Medical Society — December 5, Holiday House, St. Peter, 6:30 p.m.

Scott-Carver County Medical Society — December 6, Wagner's Colonial Club, Jordan, 7:30 p.m.

Camp Release District Medical Society — December 8, Hunt Hotel, Montevideo, 6:30 p.m.

St. Louis County Medical Society — December 8, Ex. Comm. at 6:00 p.m., St. Luke's Hospital, Duluth.

Minnesota Academy of Medicine — December 14, Town & Country Club, St. Paul, 6:30 pm.

St. Louis County Medical Society — December 17, Annual banquet, dance; Kitchi-Gammi Club, Duluth, 7:30 p.m.

JANUARY

Southwestern Minnesota Medical Society — January 2, Worthingon, 7 p.m.

Zumbro Valley Medical Society — January 4, Mann Hall, Rochester, 8:00 p.m.

Hennepin County Medical Society and Hennepin County Academy of General Practice — January 9, Pick-Nicollet Hotel, Minneapolis, 6:00 p.m.

Brown County Medical Society — January 10, Orchid Inn, Sleepy Eye, 7:00 p.m.

Minnesota Academy of Medicine — January 11, Town & Country Club, St. Paul, 6:30 p.m.

Camp Release District Medical Society — January 12, Hunt Hotel, Montevideo, 6:30 p.m.

St. Louis County Medical Society — January 12, Ex. Comm. at 6:00 p.m.; annual business meeting at 8:00 p.m., St. Mary's Hospital, Duluth.

Blue Earth Valley Medical Society — January 18, Interlaken Golf Club, Fairmont.

Twin City Urological Society — January 20, 6:00 p.m. Town & Country Club, St. Paul.

Range Medical Society — January 24, Ex. Comm. & annual meeting; 7:00 p.m. dinner, meeting follows, Hibbing.

National Winter Sports Injury Conference — January 27-29, University of Wisconsin Medical School, Wisconsin Center, Madison, Wisconsin.

Ramsey County Medical Society — 8:00 p.m. — January 30, 15th floor, Lowry Medical Arts Bldg., St. Paul.

ANNOUNCEMENTS

Minnesota Obstetrical-Gynecological Society Meeting, December 3rd, Hennepin County General Hospital. Contact: Theodore Watson, M.D., 1261 Lowry Medical Arts Building, St. Paul.

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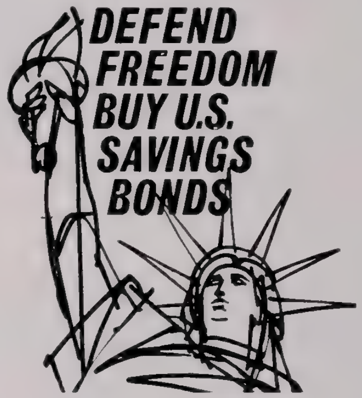

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INTERNIST for 20-physician-clinic in prosperous Minnesota city. Salary negotiable first year, then full partnership. East Range Clinic, Virginia, Minnesota.

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Registration for each of these sessions is limited . . . be sure you don't miss out on the program of your choice by using the form below to register in advance. Because of the space limitation, please include a $10 registration fee for each postgraduate course you select.

DETAILS OF THE SESSIONS:

OBSTETRICS AND GYNECOLOGY

Monday thru Wednesday, Nov. 28-30, 9 a.m.-12 noon
Course Director and Moderator:
  Daniel G. Morton, M.D.
  Professor and Chairman, Dept. OB-GYN
  UCLA
Including 30-minute presentations on:
  Management of Septic-Abortion
  Intrauterine Transfusion for Erythroblastosis Fetalis
  Hypertensive Disorders in Pregnancies
  Human Sterilization: Indications, Legal Implications, Methods
Each presentation will be followed by a 10-min. discussion period.

CARDIOVASCULAR DISEASE

Monday thru Wednesday, Nov. 28-30, 2-5 p.m.
Course Director:
  George C. Griffith, M.D.
  Emeritus Professor of Medicine
  University of Southern California, Los Angeles
Recent Advances in Operable Cardiovascular Disease
Pulmonary Embolism: Prevention, Recognition, Treatment
Regional Arteriosclerosis
Each half-day session will be followed by a 30-minute panel discussion by all participants.

FLUID AND ELECTROLYTE BALANCE

Monday thru Wednesday, Nov. 28-30, 9 a.m.-12 noon
Course Director:
  Telfer B. Reynolds, M.D.
  Professor of Medicine
  University of Southern California School of Medicine
30-minute presentations on:
  Basic Concepts in Fluid and Electrolyte Balance
  Dehydration and Uremia
  Hyponatremia
  Hypokalemia and Hyparkalemia
  Normal Acid-Base Balance
  Acidosis and Alkalosis
Each morning's program will feature a 90-minute panel discussion.

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GENERAL PRACTITIONER WANTED to associate with solo practitioner currently doing over $100 M annual volume. Guaranteed minimum salary, plus bonus. Central Minnesota Lake Region. Write: MINNESOTA MEDICINE-364, 496 Lowry Medical Arts Building, St. Paul 55102.

THREE MAN group in North West Wisconsin Resort, State Conservation and Retirement Area needs two more physicians adequately to serve their practice. Facilities offered are three-room physician suites, X-ray and lab under AMT technician, RN-only nursing personnel. New accredited thirty-two bed hospital and forty-six bed nursing home. Deer and duck hunting, fishing within five minutes of town. Internist most needed; generalists welcomed. Will meet any reasonable salary request. Partnership after one year. Write: MINNESOTA MEDICINE-365, 496 Lowry Medical Arts Building, St. Paul 55102.

RESIDENTS IN PSYCHIATRY — Opening for January 1, 1967 and July 1, 1967. Stipend $11,400 for physicians just completing internship. Federal stipend available to physicians with 4 years non-psychiatric training or experience following internship amounting to $12,000 annually with an extra $3600 tax exemption. Graduates of American schools must be eligible for Iowa licensure. Foreign graduates must have ECFWG certificate. Hospital has 450 in-patients, large out-patient dept., children's unit with Board-certified Child Psychiatrist. Eclectic program with emphasis on community and existential psychiatry. Thirteen senior staff members including ten Board certified. Numerous consultants. Authorized for 12 residents. Affiliation with University of Iowa. Enthusiastic and dynamic training and treatment programs that are best understood by a personal visit. Write or call collect: W. C. Brinegar, M.D., Supt., or John Worthington, M.D., Mental Health Institute, Cherokee, Iowa.

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WANTED: Young general practitioner to join five-man group consisting of three GPs, a general surgeon, and radiologist. College town serving population of 22,000 30 miles from Twin Cities. Also need LOCUM TENENS in general practice. Contact: Ed Jenkins, Manager, River Falls Medical Clinic, River Falls, Wisconsin, Phone 425-5322.

PSYCHIATRIST (or interest in psychiatry) and general physician. 1,300 bed NP hospital with progressive treatment, full supporting staff. Community of 35,000 in hunting and fishing area, three colleges, 1½ hours from University of Minnesota. Salary range $15,000-$20,000 depending on qualifications. Liberal fringe benefits. Financial assistance in moving. License in one of the States, United States, required. Nondiscrimination in employment. Write Chief-of-Saff, VA Hospital, St. Cloud, MN 56301.

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WANTED: General surgeon, qualified or certified. Six man group in Minnesota. Fully accredited 150 bed hospital, open staff. Further information available. Write: Falls-Starekow Clinic, Thief River Falls, Minnesota. 56701.

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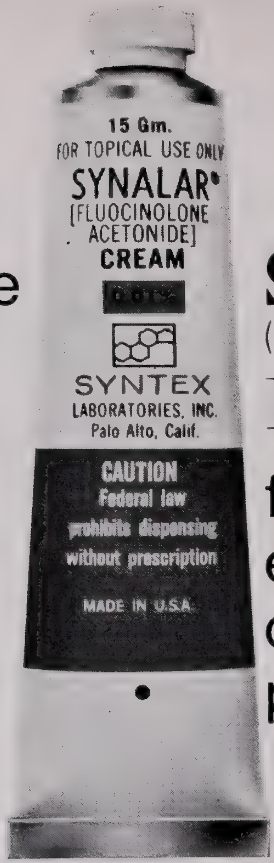
No matter how noble the objectives of a government, if it blurs decency and kindness, cheapens human life, and breeds ill will and suspicion — it is an evil government. — Hoffer.



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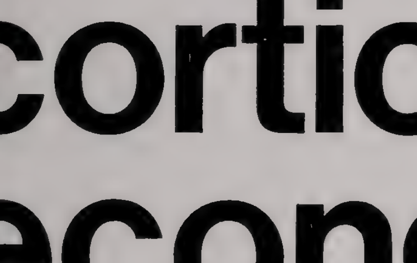
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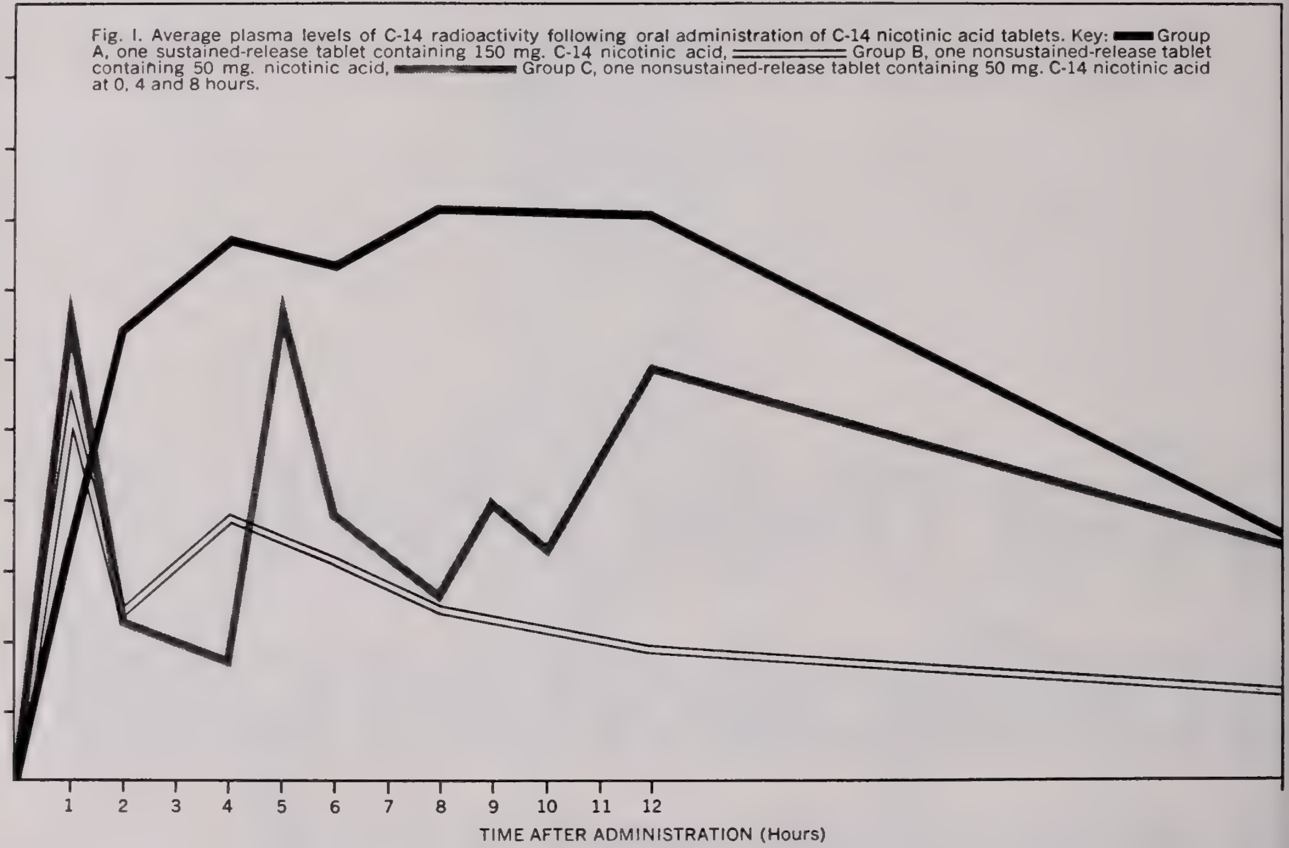
Fig. I. Average plasma levels of C-14 radioactivity following oral administration of C-14 nicotinic acid tablets. Key: ▬ Group A, one sustained-release tablet containing 150 mg. C-14 nicotinic acid, ═ Group B, one nonsustained-release tablet containing 50 mg. nicotinic acid, ▬ Group C, one nonsustained-release tablet containing 50 mg. C-14 nicotinic acid at 0, 4 and 8 hours.

(fewer absent doses by absent-minded patients)

Human volunteer subjects were administered Geroniazol TT tablets with the nicotinic acid component made radioactive with C-14. Plasma and urine samples were analyzed. (See Figures I and II) The radioactive tracer study substantiated the previous clinical evidence that the release of nicotinic acid from the Geroniazol TT tablet produced a gradual rise in plasma levels to a plateau for a total of 12 hours and more.

Such proven sustained activity makes the management of geriatric patients much easier by minimizing the possibility of neglected doses through absent-mindedness or senile confusion. Therapy *can* be continuous on a daily dose of only one Geroniazol TT tablet every 12 hours.

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Geroniazol TT improves the typical, unfortunate, signs of senile confusion. Patients become more alert,

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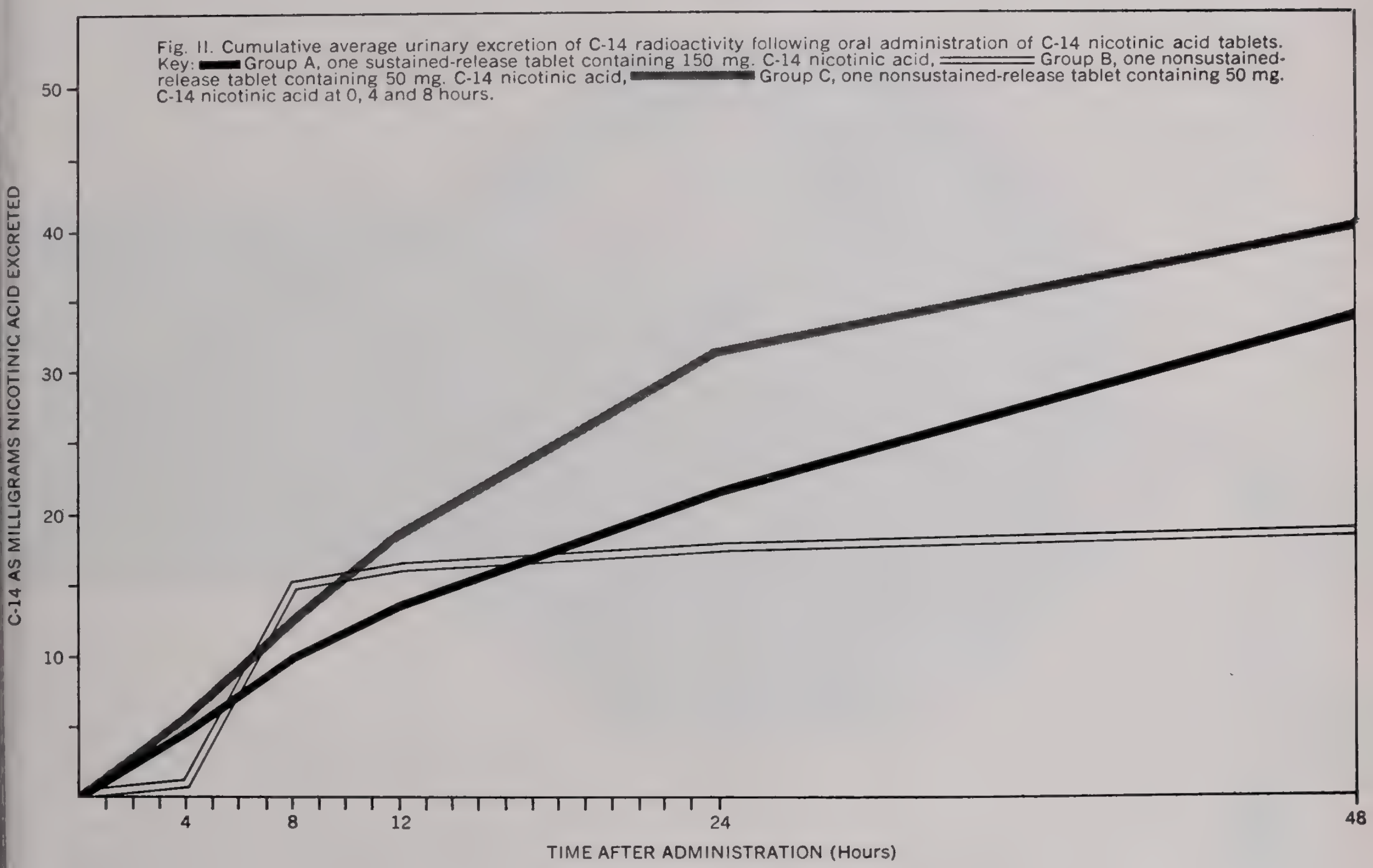

Fig. II. Cumulative average urinary excretion of C-14 radioactivity following oral administration of C-14 nicotinic acid tablets. Key: ▬ Group A, one sustained-release tablet containing 150 mg. C-14 nicotinic acid, ═ Group B, one nonsustained-release tablet containing 50 mg. C-14 nicotinic acid, ▬ Group C, one nonsustained-release tablet containing 50 mg. C-14 nicotinic acid at 0, 4 and 8 hours.

less confused and moody. Personal care, memory, emotional stability, social attention improve. Fatigue, apathy and irritability are reduced.

A prescription for 100 tablets of Geroniazol TT will permit your patients to enjoy the benefits of time-prolonged nicotinic acid/pentylenetetrazol therapy, at an economical price. Dosage is only one tablet every 12 hours.

Contraindications: There are no known contraindications.

Precautions: Exercise caution when treating patients with a low convulsive threshold.

Side Effects: Side effects are rarely encountered, however due to the vasodilatation effect of nicotinic acid, transitory mild nausea, flushing, tingling and pruritus are possible.

Dosage: One tablet every 12 hours.

Supplied: Prescribe bottles of 100 tablets, to take advantage of recent price reduction.

References: 1. Report by Nuclear Science & Engineering Corp., Pittsburgh, Pa., in files of Philips Roxane Laboratories. 2. Connolly, R.: W. Virginia Med. J. *56*:263 (Aug.) 1960. 3. Curran, T. R., and Phelps, D. K.: Am. Pract. & Digest Treat. *11*:617 (July) 1960.

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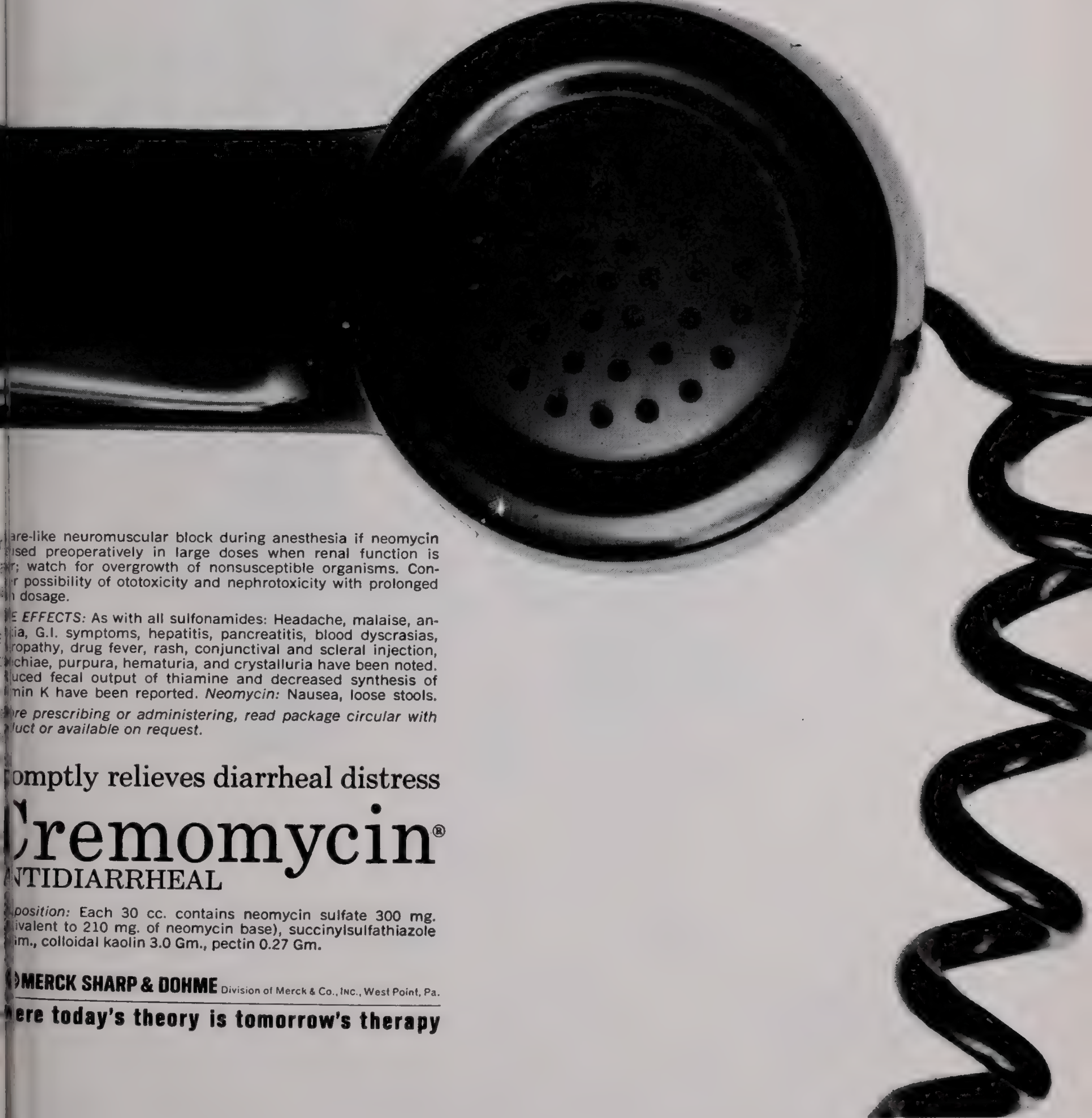
CONTRAINDICATIONS: Do not use in intestinal obstructic tensive ulceration of bowel, or diverticulosis; in hypersen to sulfonamides or neomycin; in pregnancy at term, in pren infants, or during first week of life in the newborn.

WARNINGS: Use only after critical appraisal in patient hepatic or renal damage, urinary obstruction, or blood c sias. Fatal hypersensitivity reactions and blood dyscrasi ported with use of sulfonamides. Consider periodic blood c hepatic and renal function tests during intermittent or c use.

PRECAUTIONS: Succinylsulfathiazole: Use with caution if is history of significant allergies and/or asthma. Continu requires supplementary vitamins B_1 and K. *Neomycin:* Wa

your ℞ for Cremomycin can provide relief



are-like neuromuscular block during anesthesia if neomycin ised preoperatively in large doses when renal function is r; watch for overgrowth of nonsusceptible organisms. Con- r possibility of ototoxicity and nephrotoxicity with prolonged dosage.

E EFFECTS: As with all sulfonamides: Headache, malaise, an- ia, G.I. symptoms, hepatitis, pancreatitis, blood dyscrasias, ropathy, drug fever, rash, conjunctival and scleral injection, chiae, purpura, hematuria, and crystalluria have been noted. uced fecal output of thiamine and decreased synthesis of min K have been reported. *Neomycin:* Nausea, loose stools.

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position: Each 30 cc. contains neomycin sulfate 300 mg. ivalent to 210 mg. of neomycin base), succinylsulfathiazole m., colloidal kaolin 3.0 Gm., pectin 0.27 Gm.

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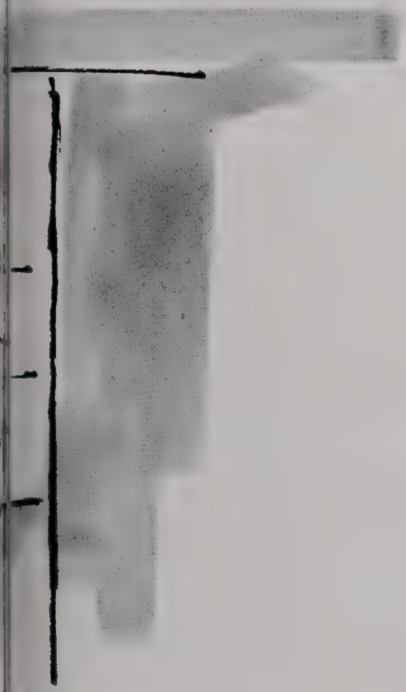
ere today's theory is tomorrow's therapy



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Use cautiously in individuals with severe hypertension, diabetes mellitus, hyperthyroidism or urinary retention. Caution adults who operate machinery or motor vehicles that drowsiness may occur. Each Melet contains phenylephrine hydrochloride 10 mg. and chlorpheniramine maleate 2 mg.

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against the usual gram-negative urinary pathogens

Why use five...where **one** will do?

In a recent 217-patient hospital study,[1] urinary tract infections were treated with a variety of widely prescribed antimicrobial agents including: a sulfonamide (40 patients), chloramphenicol (20 patients), nitrofurantoin (33 patients), nalidixic acid (30 patients), tetracycline (27 patients), colistimethate sodium (22 patients)... and 2 combinations of 5 agents each (45 patients). The 2 combinations were selected to afford maximal theoretical antibacterial coverage against the usual urinary pathogens. They were (1) tetracycline, chloramphenicol, nitrofurantoin, ristocetin and polymyxin B; and (2) tetracycline, chloramphenicol, erythromycin, nitrofurantoin and colistimethate sodium.

This clinical study shows that the two combinations of antibiotics were not superior to some of their single components. The authors point out that antibiotic antagonism often negates theoretical advantages of multiple therapy. Coly-Mycin Injectable (colistimethate sodium) was one of the single components that was shown to be equal to the combinations and eradicated bacteriuria in two-thirds of the patients.

Theoretical choice of multiple antibacterial therapy has been shown to be no more effective than one well-chosen agent which also offers least patient exposure to possible side reactions, toxicities, allergic manifestations and higher drug costs.

1. McCabe, W. R., and Jackson, G. G.: New England J. Med. 272:1037, 1965.

in gram-negative urinary tract infections often the single well-chosen agent

COLY-MYCIN®
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Coly-Mycin® Injectable

(colistimethate sodium)

Indications: Especially indicated for the treatment of severe acute and resistant chronic urinary tract infections due to sensitive strains of gram-negative organisms. Also indicated in respiratory tract, surgical, wound and burn infections and in septicemia due to sensitive organisms. Particularly indicated when any of these infections are caused by sensitive strains of *Pseudomonas aeruginosa.*

Adverse Reactions: Occasional reactions such as circumoral paresthesias, tingling of the extremities, pruritus, vertigo or dizziness may occur. Reduction of dosage may alleviate symptoms. Therapy need not be discontinued, but such patients should be observed with extra care.

Warning: Patients should be cautioned not to drive vehicles or use hazardous machinery while on therapy.

Precautions: In cases of impaired or suspected renal impairment, use with greater caution and reduce dosage in proportion to extent of impairment. Transient elevations of BUN have been reported. As a routine precaution, appropriate blood studies should, therefore, be made during prolonged therapy.

As with all polypeptides, the possibility of muscular weakness, including apnea, due to inadvertent overdosage or normal dosage in the presence of impaired renal function, should not be overlooked. In cases of apnea, medication should be promptly discontinued and assisted respiration given until serum levels fall and normal breathing is restored.

Other antibiotics, such as kanamycin, streptomycin, dihydrostreptomycin, polymyxin, and neomycin, may also have varying neurotoxic or nephrotoxic potential. They should be used with great caution concomitantly with Coly-Mycin Injectable (colistimethate sodium).

For deep intramuscular injection only.

Dosage: By the I.M. route only, in 2 to 4 divided doses ranging from 1.5 to 5 mg./Kg./day (0.7 mg. to 2.3 mg./lb./day). Average adult dose is 2.5 mg./Kg./day (1.1 mg./lb./day). In the presence of bacteremia, septicemia, or other serious infection, greater than average doses may be required; however, maximum daily doses should not exceed 5 mg./Kg. (2.3 mg./lb.) where renal function is normal.

Not recommended against Proteus.

Colistin is also available (as colistin sulfate) in: Coly-Mycin® Pediatric for Oral Suspension (not for systemic use), and Coly-Mycin® Otic with Neomycin and Hydrocortisone.

Full information is available on request.

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*Multiple of adult Minimum Daily Requirement supplied.
†The need for these substances in human nutrition has not been established.

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Dosage: Adults, 1 tablespoonful; children (over 15 years old), 1 to 2 teaspoonfuls; children (4 to 15 years old), 1 teaspoonful. To be taken three times daily 30 minutes before meals.

Contraindications: As with other drugs with CNS stimulating action, Alertonic is contraindicated in hyperactive, agitated or severely anxious patients and in chorea or obsessive compulsive states.

Side effects: Reports of overstimulation have been rare. Patients who are known to be unduly sensitive to the effects of stimulant drugs should be observed carefully in the initial stages of treatment.

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1. Schleif, R.H.: J.A.PH.A., 46:179,1957 *U.S. Pat. No. 3,062,714

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Minnesota Medicine at a Glance

Surgery for Carotid Artery — Garamella et al. Page 1669

This article describes the authors' favorable experience in re-establishing blood flow in patients who have had totally occluded carotid arteries. The conclusions may be debatable, but the article is well done and should be of interest to all readers who must manage the patient with this condition.

Complications from Anticoagulants — Reece and Olson Page 1677

Most doctors who have prescribed anticoagulants for thrombophlebitis or coronary disease have observed from time to time the usual insignificant episodes of ecchymosis, which are associated findings during the course of anticoagulant therapy. For these minor episodes there is no serious concern, but the possibility of major hemorrhages which endanger the life and health of the individual must be kept in mind, lest these complications get out of hand. A review of the relatively large series of major complications, occurring over a short period of time at one hospital, suggests the nature of these complications which may be easily overlooked. Certainly anticoagulant medication should not be administered lightly and without adequate control.

Augmentation Mammaplasty — Erich Page 1685

Indications for augmentation mammaplasty by Dr. John B. Erich is an excellent outline of the reasons for performing this procedure and also emphasizes when it should not be done. As the article states, the surgeon can anticipate psychological improvement when dealing with emotionally stable women who are sensitive and embarrassed about underdeveloped breasts. On the other hand, women with complex emotional problems which they attribute to small breasts will not benefit from surgery. Although not mentioned in this article, another use for these implants is following subcutaneous mammectomy for multinodular fibrocystic disease, preferably as a delayed two-stage procedure to minimize the chance of complications.

Surgical Emergencies in Pregnancies — Swenson and Runquist Page 1701

A massive intraperitoneal hemorrhage occurring in late pregnancy is a possibility and may result from an abnormality totally unrelated to the pregnancy itself. In order that such possibilities can be kept in mind, a review of Swenson's and Runquist's case report is well worth while. This is an instance in which prompt action undoubtedly saved the life of the patient.

Computer Medicine — Collen Page 1705

Dr. Morris F. Collen predicts that the computer will have the greatest technological impact on medical science since the invention of the microscope. Computer medicine will permit mass production of more data on more people and more data on the individual person. He predicts that within ten years every large hospital will have some form of computer system. He describes a computer operation used by the Kaiser Foundation Health Plan in San Francisco and Oakland with a two to three-hour automated multiphasic screening program. It seems that computer medicine is here to stay.

Complications of Stapedectomy — Eades Page 1743

In performing surgical operations to correct hearing loss, the dreaded problem of further sensori-neural hearing loss is usually associated with excessive surgical trauma. In order to have a fuller evaluation of these possible complications, a review of the seminar by Eades should alert one to these complications and the suggested method of diminishing them.

What's New in Hematology — Hagedorn Page 1757

The trend in transfusions today is to administer only the specific fraction of blood that is needed. Whole blood transfusions are now in a category of shotgun hematinic therapy. There is considerable difficulty in distinguishing fibrinolytic states from consumptive coagulopathies. The differential is essential for proper therapy.

The Phonocardiogram in Heart Diseases — Mueller and Grismer Page 1769

Phonocardiography is a graphic method of heart sound representation and can be helpful in diagnosis of heart diseases. Crucial points of precise timing of various heart sounds and murmurs can be established by phonocardiography. This information complements the auscultatory interpretation. The article describes the normal and many of the common abnormal sounds of heart disease.

Understanding

One meets with many men who have been fine students, and have stood high in their classes, who have great knowledge of medicine but very little wisdom in application. They have mastered the science, and have failed in the understanding of the human being. — William Mayo

---

New Nervous-Mental Hospital

St. Croixdale Sanitarium, located at Prescott, Wisconsin, broke ground in August for their new patient facility. The new building will house all departments of the hospital.

St. Croixdale Sanitarium has been operating since 1928. Their medical staff consists of five psychiatrists and neuro-psychiatrists. St. Croixdale participates in the Medicare program, is listed with the American Hospital Association, and has been approved and recommended for accreditation by the Joint Commission on Accreditation of Hospitals.

To do unto others as you would have them do unto you is well; but to do unto them as they would themselves be done by is better. — Comtesse Diane

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State University of New York
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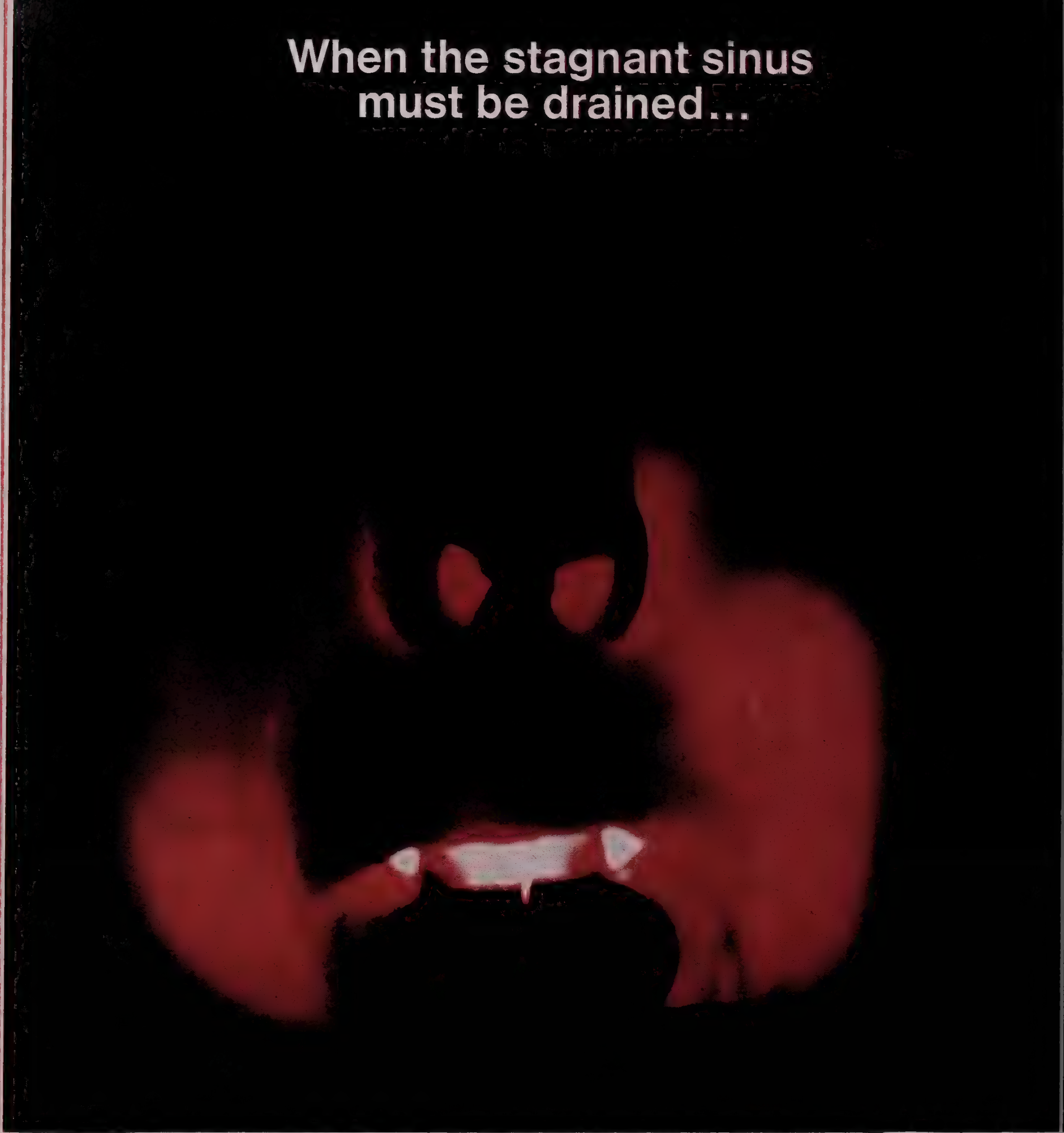

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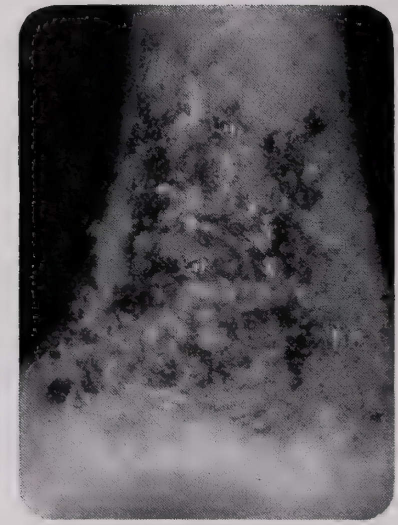

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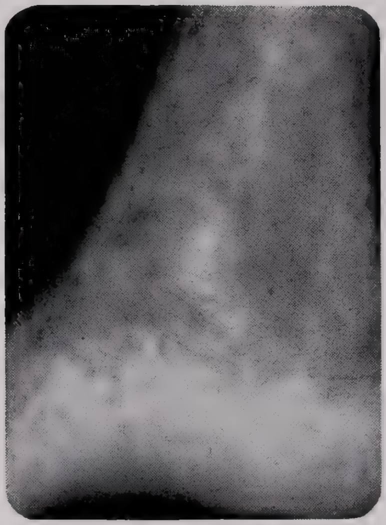

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THIS ISSUE of Minnesota Medicine commemorates the State University of New York Upstate Medical Center, recognizing, as has been done in the past with other groups, the contributions to the practice of medicine by particular institutions.

The result of this editorial policy has been a broader contributor base, a wider reader interest and further contributions to current medical literature by an already outstanding medical journal.

The physician who has an article accepted for publication in any journal usually presents a new method, a new therapy or a new explanation for known facts documented by case reports of his personal experiences and by the evidence of other prior contributions in the area of his presentation.

The reader, on the other hand, weighs the article against his own experience, his knowledge, and his awareness of the status of the author before forming a conclusion.

Some readers, not in full agreement with the author, make a contribution of their own by letters to the Editor expressing a different conclusion or a different opinion.

If the objectivity and tempered reasoning that typify these dissenters could carry into other areas of physician disagreement, medical progress in socio-economics could better parallel progress in medical science.

Regrettably the very experience and knowledge which are of aid in evaluating a scientific presentation are lacking in physician appraisal in this other area, for no physician experience in the past can be applied to physician problems of the present. As a result, rumor is sometimes substituted for reason, prejudice for fact, and personal opinion for program.

Any division of the physicians of America, any group position adopted without full awareness of physician concensus, any decision arrived at without competent legal advice, certainly any suspicion or villification directed at those physicians sincerely following a course dictated by reason, moderation and full exploration is a disservice to medicine.

As our troubled medical present leads into a more troubled future, fragmentation of medical opinion and action may be our major problem and must be our major concern.

This being the concluding President's Letter of this official term, it would be incomplete without a sincere expression of gratitude for the opportunity to be of service, however inadequate to our Association, to know better many Association members, and to further observe the competence and efficiency of Mr. Brunn and his staff.

R P Buckley M.D.

R. P. Buckley, M.D.
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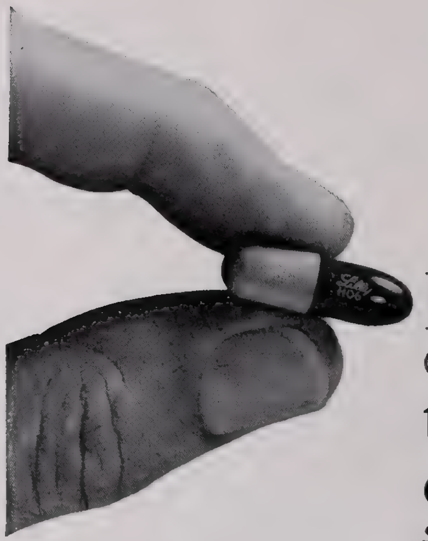

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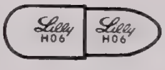	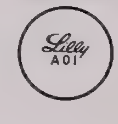	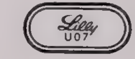	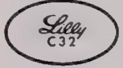	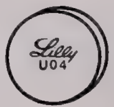

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The Crural Branches of the Phrenic Nerves*

Their Surgical Significance

MARTIN WYNYARD, M.D.
HAROLD D. KLETSCHKA, M.D.
Syracuse, New York

THE REGION of the esophageal hiatus has been of continued interest with regard to both its physiological and anatomical aspects. To understand the mechanisms controlling gastric reflux and to apply this knowledge to the treatment of hiatal herniation has constituted the principal challenge. Surgical intervention in the treatment of hiatus hernia at the present time yields inadequately predictable results, and this doubtless reflects an incomplete understanding of all the factors germane to constructing a repair that will reestablish the physiological state. Failure to study accurately the nerve supply to the crura of the diaphragm has contributed to this lack of understanding. The authors have drawn observations and conclusions based on anatomical studies that they and others have carried out. It is their hope that a presentation of this information will help to focus attention on the crural nerve supply and to stimulate thereby further clinical and experimental studies which might contribute benefit to surgical repair.

On reviewing standard anatomical texts it is apparent that information regarding crural innervation is very scanty and confusing. Most of these works of reference[1,2,3,4,5] dispose of the matter without express mention of the innervation of the crura or by simply indicating that the phrenic nerve is the sole motor nerve to its own half of the diaphragm. It is left open to question to which half of the diaphragm the esophageal hiatal musculature belongs. Illustrations do not show the innervation of the crura. In a description of the crural nerve supply found in one standard textbook[6] the following statement appears: ". . . the crura, derivatives of the prevertebral rectus, are supplied by the lower intercostal nerves, not by the phrenic."

It is obvious that an accurate understanding of the nerve supply to the crura could be very important in conceiving a proper surgical attack on hiatus herniae. A clear appreciation of this fact led Collis et al.[7] to carry out anatomical dissections to establish the pattern of innervation of the diaphragmatic crura. So far as we can determine, their report in 1954 detailed the first clear description of the crural nerve supply. They concluded that the muscle fibers arising from the right half of the central tendon (crural fibers) are innervated by the right phrenic nerve, while those arising from the left half are supplied by the left phrenic nerve. Because of this arrangement they further suggested that the fibers from the right crus which are on the left side of the esophagus are really part of the left side of the diaphragm. This arrangement is clearly understandable since the esophagus is an embryological midline structure.

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*See editorial page 1851.

Observations

We have dissected the nerve supply to the diaphragmatic crura in three cadavers. Collis[7] has clearly shown the course the branches of the phrenic nerves take to reach the crura. We undertook to demonstrate the terminal distribution of each of these branches. Merendino[8] pointed out that the crural branch almost always presents as a separate, definitive nerve trunk. In our dissections we traced these nerves macroscopically as far as we could into the crural musculature (Figures 1 and 2).

The Left Crural Nerve

The left crural nerve, after reaching the abdominal aspect of the crus approximately 1.3 centimeters to the left of the apex of the esophageal hiatus, takes a caudad course to a point approximately 4 millimeters from the rim of the hiatus at the mid-hiatal level. The principal nerve trunk continues in the same direction but assumes a position at a greater distance from the margin of the hiatus (approximately 8 millimeters) at its lowermost aspect because of the convergence of the crural musculature away from the nerve in this area. The fibers can be traced

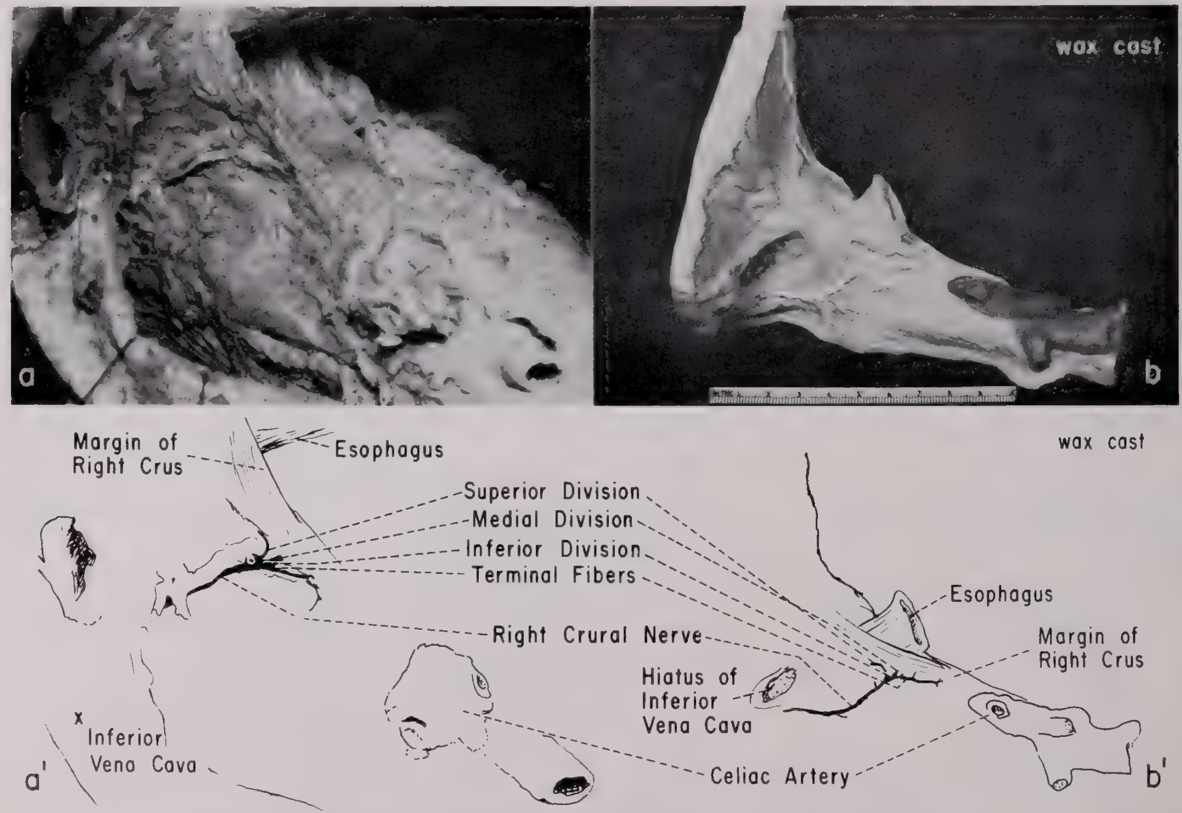
a
wax cast
b
Margin of Right Crus
Esophagus
Superior Division
Medial Division
Inferior Division
Terminal Fibers
Right Crural Nerve
x
Inferior Vena Cava
a'
Hiatus of Inferior Vena Cava
Celiac Artery
wax cast
Esophagus
Margin of Right Crus
b'

Fig. 1 — Right crural nerve showing its divisions and terminal fibers.

for a short distance (approximately 1.5 centimeters) beyond the lower level of the esophageal hiatus. At the level of the apex of the hiatus the left crural nerve leaves its superficial course on the undersurface of the diaphragm and continues within the muscle tissue approximately one millimeter below the surface. It receives a vascular accompaniment and distributes fine divisions seriatim predominantly in a medial and posterior direction.

The Right Crural Nerve

The right crural nerve reaches the right crus at the mid-hiatal level at approximately a right angle. It then enters the crus to a depth of about 1.5 millimeters on its abdominal surface and divides into a superior and an inferior division. A medial division (a tiny fiber that is traceable for only a few millimeters) quickly arises from the inferior division, and the latter then continues in a caudad direction. Initially, it is situated approximately 1.0 centimeters from the inner margin of the hiatus, but in its terminal portion this distance is reduced to about 3 millimeters. Largest of the right crural nerve divisions is the inferior division. The superior division also maintains its relationship to the hiatal inner margin.

The principal crural muscle tissue and nerve supply lie lateral and inferior to the esophagus. This anatomical arrangement is undoubtedly of physiological importance and of interest to the surgeon. Photographic demonstration of the anatomy of this region, while maintaining the in-situ structural relationships (Figures 1-a and 2-a), presented technical problems, and a wax cast was therefore prepared to overcome these difficulties and is photographically depicted in Figures 1-b and 2-b.

Discussion

The surgical significance of the crural nerves relates to their vulnerability as a consequence of their anatomical location and distribution, particularly in their terminal course. The left crural nerve during its initial course while gaining access to the crus is a superficial structure and can very easily be injured. For the most part, each

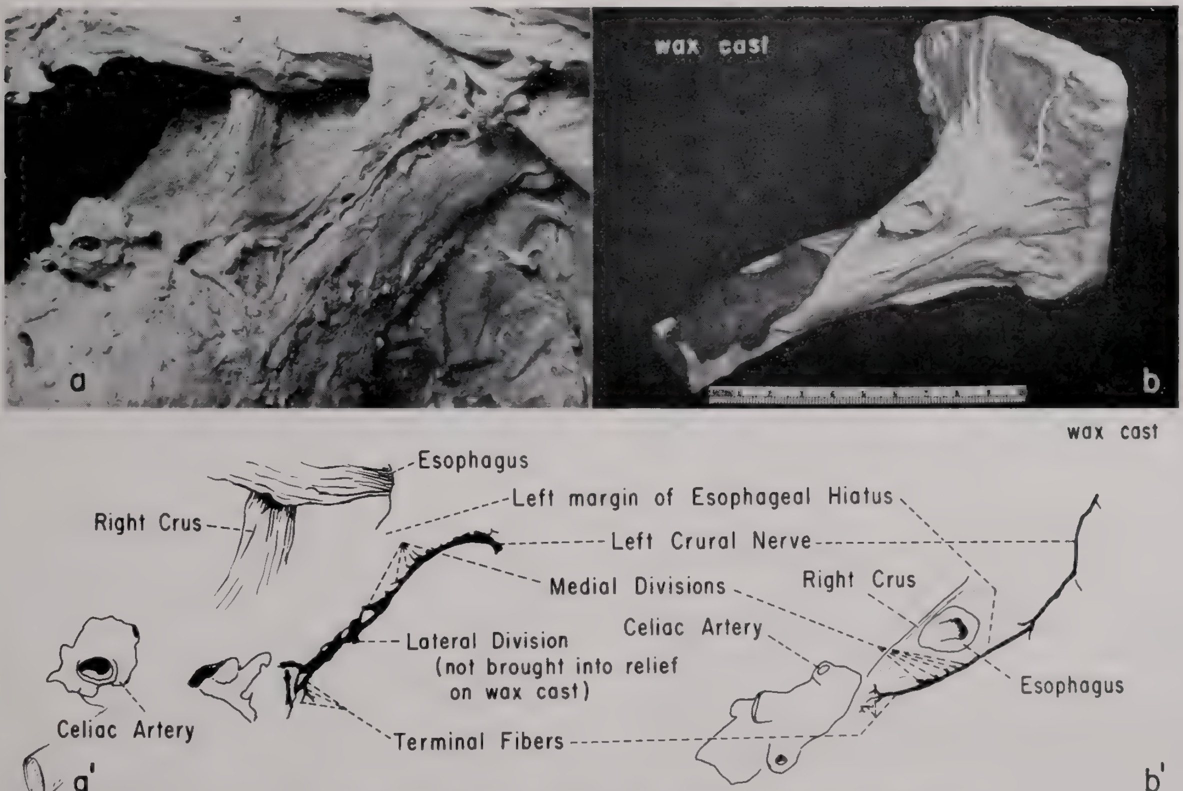

Fig. 2 — Left crural nerve showing its divisions and terminal fibers.

nerve occupies a position within the crura which is caudad to the mid-esophageal hiatus level and in close association with the hiatal margin. *Therefore, in dealing surgically with the esophageal hiatus, injury to the terminal branches of the crural nerves is most likely to occur in those instances in which the hiatus is closed posteriorly to the esophagus.* Furthermore, because of the superficial course the nerve fibers take on the abdominal aspect of the crura, an abdominal approach increases the hazard in such repairs. The close relationship that the terminal ramifications bear to the margin of the esophageal hiatus make it almost impossible to close the hiatus posterior to the esophagus from the abdominal aspect without incorporating these nerve fibers in the suture. At least it would suggest the loose application of the sutures or the employment of absorbable material.

In cases we have reoperated for hiatus hernia we have been impressed by the atrophy and scarring which takes place in the crura when the previous surgical efforts have been directed to this vulnerable region. Such cases often come to reoperation because of persistence or recurrence of reflux esophagitis following the initial repair. Infections and other disease processes (possibly secondary to hiatus hernia repair) in this region can result in destruction of these superficially situated nerve fibers with resultant muscle atrophy and a disturbance of the physiological state. The same consequences can result from an unskillfully performed abdominal vagectomy in which injury occurs to these nerve fibers.

In patients presenting with symptoms of reflux esophagitis it is important to determine whether previous injury to the phrenic nerve has occurred. Strauss[9] has shown that crushing of a phrenic nerve in man results in eventual complete atrophy of the ipsilateral hemidiaphragm. In surgical procedures within the lower thorax care must be exercised to preserve the posterior branch of the phrenic nerve if injury to the corresponding crus is to be avoided. Selective phrenic nerve paralysis with preservation of this branch has been utilized by Collis[10] in designing a surgical repair for hiatus hernia.

Summary

The terminations of the crural branches of the phrenic nerves are described and illustrated. Based on the pattern of innervation we propose that crural musculature to the left of the esophagus be referred to and considered as the left crus; and the crural musculature to the right of the esophagus, in similar manner, be identified as the right crus. The terminal branches of the crural nerves are distributed principally to that portion of each crus situated caudad to the mid-level of the esophageal hiatus and are in close association with the margin of that hiatus. The surgical significance of this pattern of distribution is discussed.

Acknowledgments

We are indebted to Dr. Philip B. Armstrong for making available to us facilities for carrying out the cadaver dissections. Dr. Warner S. Hammond has rendered invaluable advice and assistance regarding descriptive terminology and analyses bearing on the embryological and anatomical validity of our observations. We wish to thank Mr. Allen G. Ayres for the work he has contributed in making the wax cast and in providing illustrations. Our appreciation is extended to Mr. Charles G. Reiner and Mr. Paul A. Tackman for photographic work.

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In a war of ideas it is people who get killed. — Lec

Shearing Injuries of the Subcutaneous Tissues

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VISIBLE LACERATIONS and abrasions of the skin can be recognized by simple inspection. Injuries of bone can generally be recognized because of structural deformity, pain or interference with function. In contrast to this ease of diagnosis, the early signs and symptoms of the shearing injury which involves the tissues between the skin and underlying fascia or bone may be minimal, and the diagnosis becomes obvious only after the development of complications. In order to avoid these complications, awareness, early diagnosis and prompt appropriate treatment are essential.

Pathogenesis

A tangential force applied to the surface skin carries it over the underlying fascia or bone with resultant tearing of the intermediate tissues. The contusion or abrasive injury to the skin may be negligible. The force which shifts the skin tears the fat and, more importantly, the blood vessels. The thinner-walled veins are more likely to be involved. The smaller vessels may be injured and may ultimately thrombose. Fat necrosis may result.

The shearing force, having torn the tissues, creates a potential dead space, in which blood, serum or liquefied fat can collect. The stage is now set for the complications which not only make the diagnosis obvious but are responsible for significant morbidity.

Infection

The collection is an excellent culture medium. The byproducts of the growth of organisms may produce generalized symptoms such as fever, chills and malaise or may produce local involvement with pain, tenderness, increased swelling, induration and cellulitis. Progression to necrosis of

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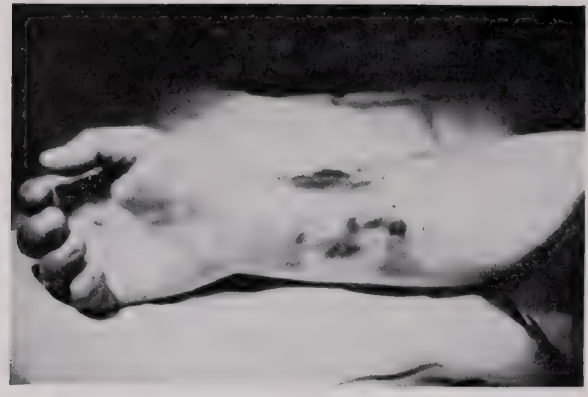

Fig. 1 — Wringer injury of forearm four days after accident. Note swelling, discoloration and skin necrosis.

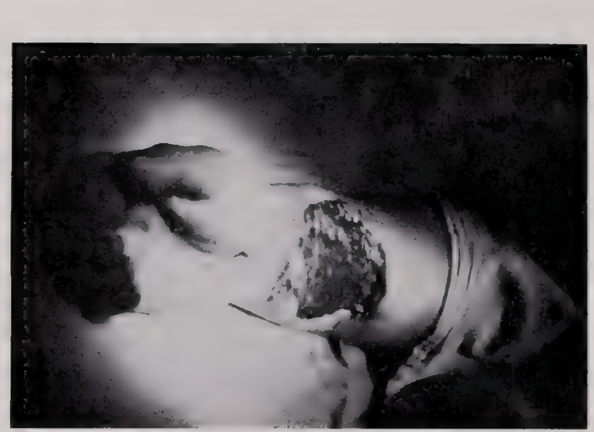

Fig. 2 — After one week a fine granulating wound is noted which is suitable for skin grafting.

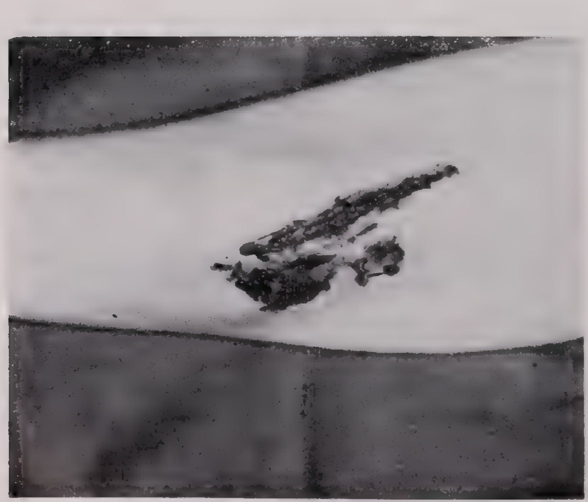

Fig. 3 — Irregular cutaneous necrosis of the pretibial area.

varying degree of the overlying skin may ensue.

Necrosis of the Overlying Skin Without Infection

The minimally traumatized skin, if allowed to return to contact with the viable bed from which it has been separated, will remain viable, and in the ordinary course of wound healing, the skin will be re-vascularized from the underlying base.

If, on the other hand, this minimally traumatized skin is elevated from the base by blood, serum, or liquefied fat collected in the dead space, revascularization from the base cannot occur. The deprivation of the skin over the collection is associated with progressive edema, progressive thrombosis of the previously minimally injured vessels, and necrosis of the skin with full thickness loss.

Treatment

Proper care of such an injury requires the recognition of the nature of the undermining and the potential for the formation of a collection of serosanguineous fluid or other tissue products in the dead space. This requires close observation and a high index of suspicion.

Once the collection has been recognized, it should be evacuated promptly before the insidious process of progressive damage to the overlying skin develops.

The early changes are often reversible if the elevated skin can be maintained in contact with the vascular bed after evacuation of the collection. Recurrence of the collection may be prevented by suction catheter drainage or pressure dressings depending upon the location and character of the injury.

* * *

The wringer injury is the classical example of this type of injury.

Case Reports

Case 1.

A sixty-two-year-old woman had caught her right hand and forearm in the wringer of her washing machine four days prior to examination. At the time of injury a capable general surgeon's examination showed minimal skin damage and no evidence of hematoma in hand or forearm. He applied a pressure dressing and re-examined the patient two days later. She had had no discomfort during the two-day interval.

Examination (Figure 1) showed edema of the tissues of the forearm and hand, with fluctuance on the dorsum of the hand. There was tense fluctuance on the flexor aspect of the distal forearm with blistering of the skin over a 10-cm. area on the flexor aspect. There was black necrosis of a segment of skin 2.5 × 6 cm. in size at the junction of the middle and lower thirds of the flexor aspect of the forearm. Movement of the hand, wrist and forearm was only slightly limited by the tenseness of the tissues.

At operation, the necrotic skin on the flexor aspect of the forearm was excised. Serosanguineous material gushed from the subcutaneous tissues. The fat in the subcutaneous region had been partially avulsed and was unattached beneath the skin. This was removed. Dorsal incisions were made in the second, third and fourth web spaces. Through these 2-cm. stab wounds, serosanguineous material was evacuated. Penrose drains were inserted to maintain drainage. The entire forearm and arm were wrapped in a bulky dressing. An anterior plaster slab splint was used to immobilize the area. Seven days later the skin on the dorsum of the hand and the flexor aspect of the forearm was nicely seated on the underlying tissues. A good granulating base was present (Figure 2). The defect at the site of removal of the necrotic skin was repaired with a split-thickness skin graft. Uncomplicated healing resulted.

* * *

An injury of the extremity not involving deeper structures and similar to the wringer injury of the upper extremity can frequently be recognized.

Case 2.

A seventy-three-year-old patient fell three weeks prior to admission with a resultant soft tissue abrasion on the left leg. Marked bruising and swelling were noted, but the skin appeared to be intact. There was a gradual darkening of the skin overlying the swollen area. Examination showed a doughy consistency on palpation with irregular areas of frank cutaneous necrosis (Figure 3).

At operation the eschar was broken away from the normal skin and a small amount of old dark blood ran freely from the wound. The eschar was excised sharply. The posterior aspect of the eschar was noted to have adherent currant-jelly clot. The base of the wound was filled with a clot measuring approximately one inch in thickness and extending well out into the soft tissue and beneath the skin which had been elevated from the base. All of the clot was removed and the wound was irrigated thoroughly (Figure 4).

A thin split graft was applied to the resultant open wound.

Redressing after one week showed a complete take with healing of the wound.

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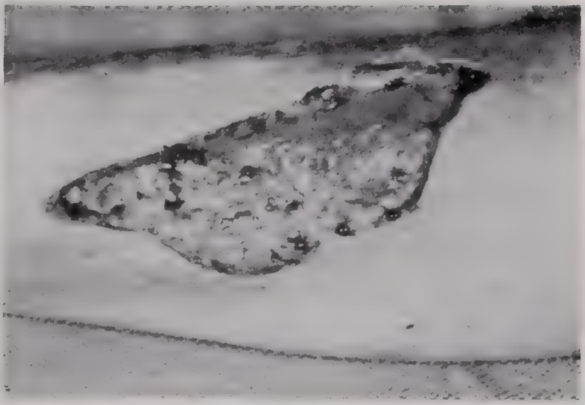

Fig. 4 — Removal of the clot and irrigation result in flattening of the cutaneous surface. This wound is ready for grafting.

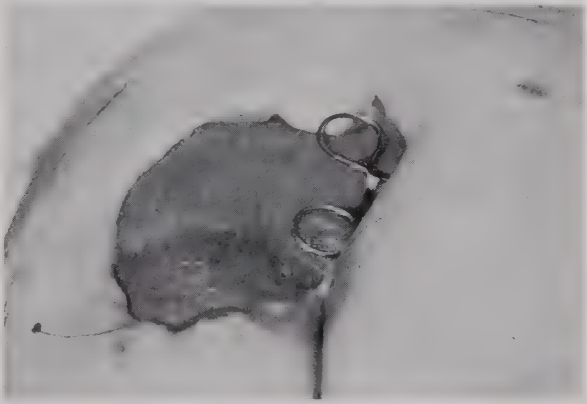

Fig. 5 — Granulating wound with Kelly clamp inserted beneath the undermined flap of the right buttock. Prompt evacuation of this hematoma prior to necrosis of the skin would have decreased this patient's morbidity.

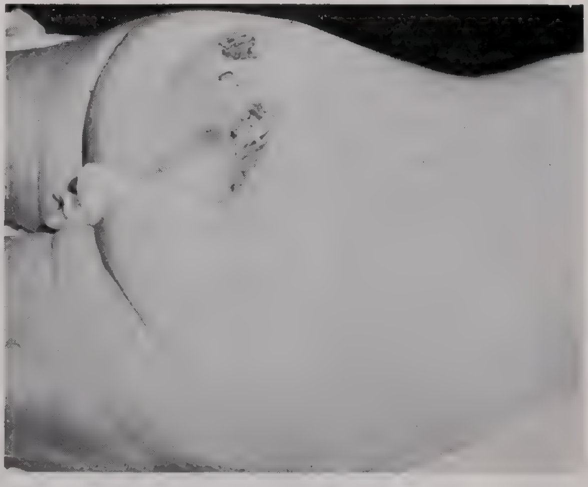

Fig. 6 — Shearing injury of the sacral area. Note the minimal involvement of the skin; yet there is a sizable hematoma.

On occasion, the injury may be completely unrecognized until late after the development of complications.

Case 3.

A fifty-year-old woman, involved in an auto accident, was admitted to the hospital for observation because of some contusions and general discomfort. No specific injuries were noted. Because her husband was more seriously injured and the patient had no place to go locally, she remained in the hospital with no significant complaints other than general discomfort.

On the sixth day following injury, the patient began to develop a low grade temperature elevation, which persisted and increased in severity without apparent cause. Two weeks following injury, redness and increased tenderness and swelling were noted in a contused area of the sacral region. Eighteen days following the injury, there was necrosis of the skin over the sacral area with associated inflammation and underlying fluctuance. On the twentieth day following injury, the area of necrotic skin was debrided. A copious amount of foul-smelling sanguinopurulent material with liquefied fat was evacuated. In the days following this procedure, a dressing program was instituted to promote healing. Consultation was requested three weeks later, at which time examination showed a skin defect 10 × 15 cm. in size overlying the sacral and coccygeal area. The bed of this defect was granulation tissue. The skin edges were undermined for a distance of from 6 to 15 cm., with the greatest area of undermining in the region of the right buttock where involvement extended laterally to the right trochanteric area (Figure 5).

Six weeks following the original injury and twenty-two days after the debridement and drainage, an operation was performed to remove the granulation tissue of the undermined area. Primary closure of the defect was performed. The sacral wound healed well. The patient was dismissed from the hospital three weeks after repair of the defect.

* * *

Case 4.

A moribund patient with general systemic problems developed a large fluctuant mass over the sacral coccygeal area with minimal superficial skin changes (Figure 6).

Comments

Not infrequently the decubitus of a paraplegic or a moribund patient may in fact be the result of shearing forces exerted on the tissues rather than due to simple ischemia from pressure, as the word pressure-sore implies. The shearing force may be more prolonged and repeated. This is particularly common in the sacral area. The patient is placed sitting in a chair or in bed with the head of the bed elevated. The body slides down or slumps due to the effects of gravity, the skin remaining fixed at its point of contact with the chair or bed. The underlying skeletal (sacral coccygeal) area moves away and a resultant tear occurs in the subcutaneous tissues. It seems likely that there is also some effect in the form of pressure ischemia as well as tension ischemia, producing death of the intermediate tissues. This is the type of mechanism which produces the bulging, inflamed fluctuant mass over the sacrum or sacral coccygeal area, not associated with necrosis of the overlying skin in the early stages.

Conclusion

Early recognition and prompt adequate treatment can prevent the complications and thereby reduce the morbidity of this type of injury.

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Oliver Wendell Holmes to the Young Practitioner

I warn you against all ambitious aspirations outside of your profession. Medicine is the most difficult of sciences and the most laborious of arts. It will tax all your powers of body and mind if you are faithful to it. Do not dabble in the muddy sewer of politics, nor linger by the enchanted streams of literature, nor dig in far-off fields for the hidden waters of alien sciences. The great practitioners are generally those who concentrate all their powers on their business. If there are here and there brilliant exceptions, it is only in virtue of extraordinary gifts, and industry to which very few are equal.

Tomography* of the Respiratory Tract

Use of Polytome

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THE PHILIPS-MASSIOT Polytome is designed and engineered so that a wide range of tomographic techniques is available for clinical exploitation. Therefore a thorough knowledge of the technical considerations is necessary in order to tailor the tomographic examination most satisfactorily to the problem at hand. It is our purpose to emphasize the advantages and disadvantages of the various unique features of this equipment as they apply to the respiratory tract so that thoughtful technical planning of the examination will produce the best results.

The Polytomographic Technique

This unit offers several pluridirectional motions for tomography. The most complex movement, the hypocycloidal* motion, produces thin sections (1.3 mm.) of fine detail. The efficient blurring effect results in a tomogram virtually free of disturbing parasite shadows. However, the hypocycloidal motion requires an exposure time of six seconds (Figure 1).

In addition, the Polytome permits linear, elliptical, and circular tomographic movements with exposure times of three seconds for the elliptical and circular motions and .4 to 1.5-second exposures for linear motion. Because the machine allows one to select the direction of the long axis of the linear and elliptical motion, maximum blurring can be obtained by orienting the long axis perpendicular to the major axis of the dominant shadows to be erased, without changing the usual patient position on the table.

Disadvantages

Disadvantages become apparent in apply-

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*See Test Your Word Score Page 1855.

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This investigation was supported in part by the John A. Hartford Foundation.

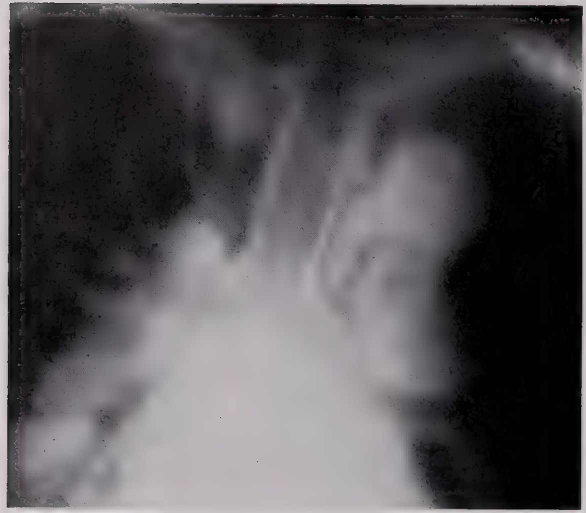

Fig. 1 — *Pneumomediastinogram.* This section was made 11.5 cm. from the table top with the patient supine. Hypocycloidal motion was used. Multiple discrete mediastinal lymph nodes are visible. The erasure of extraneous shadows lying out of the plane of interest is noteworthy.

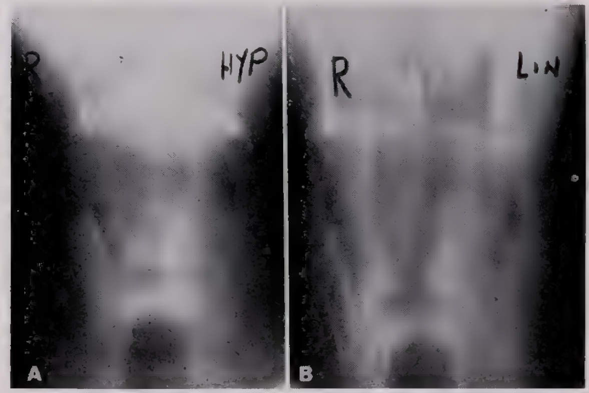

Fig. 2 — *Laryngeal tomograms.* Patient phonating and tomogram made 18 cm. anterior to the table top. (a) Hypocycloidal motion (6 secs.) 55 KVP, 100 MA. Despite low KV and close coning there is inferior contrast and lack of detail because of the long exposure. (b) Linear motion, 50° arc (1.3 secs.), 70 KV, 150 MA. Detail is superior and the blurring of extraneous shadows adequate.

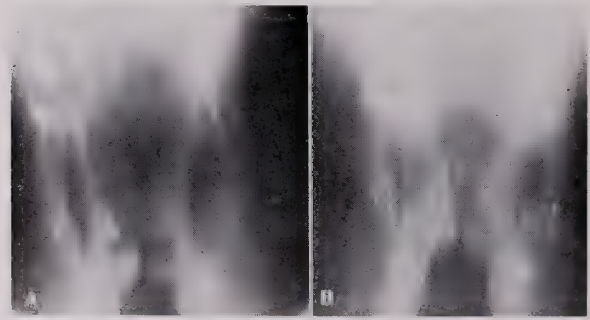

Fig. 3 — *Laryngeal tomograms.* AP sections made 14 cm. anterior to the table top. Linear motion was used. There is a small mass on the right vocal cord. (a) Inspiratory phonation. (b) Phonation.

ing the most highly refined motion to various problems in the respiratory tract. The hypocycloidal motion can be used only where absolute immobility of the part is possible. For example, the phonating larynx, the pulsating heart and blood vessels, and a very sick patient unable to cooperate frequently prevent the use of hypocycloidal motion.

The Efficient Blur

The efficient blur produced by hypocycloidal motion in the regions above and below the plane of interest results in an over-all grayness of the tomograms. This can be minimized by using low KV and high MAS and by decreasing scatter with cones. The lack of contrast may be especially troublesome in regions where the contrast is already low. This is true in tomography of the larynx because the soft tissues do not contrast well with the relatively narrow laryngeal air column (Figures 2 and 3).

Localization of Small Lesions

The thinness of the cut made by the hypocycloidal motion may make initial localization of small pulmonary shadows difficult. Frequently, thicker linear cuts are needed for localization purposes; then thin hypocycloidal sections are used for detailed analysis (Figures 4-a and 4-b).

"Satellite shadows" result when using complex motions and may be very troublesome. They represent the outer limits of the dispersed shadows of the structures which lie out of the plane of interest and are especially evident where there is considerable difference in density of the parts being examined, e.g., ribs and lung. They are especially conspicuous in the vicinity of the lateral chest wall and are produced by the axillary portions of the ribs when a lesion in this location is under study. This problem can be minimized if the point of interest is centered under the central ray even though a portion of the exposed field extends beyond the chest wall. If the "satellite shadows" hamper interpretation, one may resort to the linear motion, sacrificing some detail and accepting some interfering blur shadows (Figure 5).

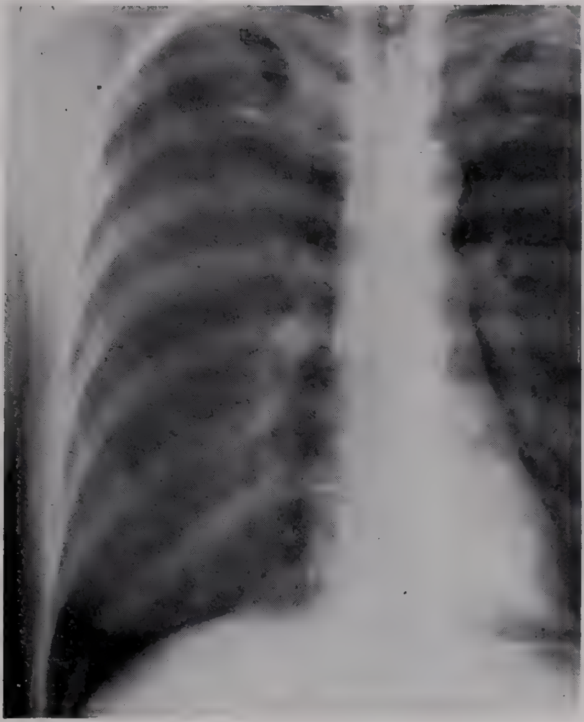

Fig. 4-a — *PA Chest.* A small nodule is visible in the right lower lung field just medial to the anterior end of the fourth rib.

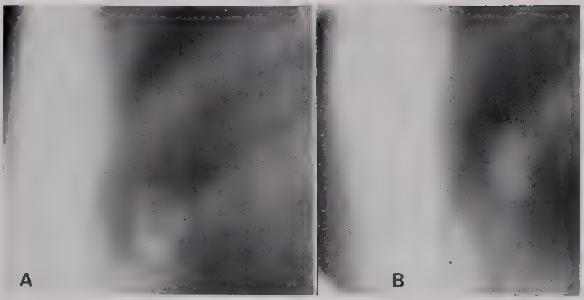

Fig. 5 — Subpleural peripheral pulmonary nodule proven to be carcinoma. (a) Linear cut. (b) Hypocycloidal cut. The detail is better on the hypocycloidal cut. The interference by the satellite shadows of the axillary portions of the ribs was minimized by centering over the lesion rather than the center cf the thorax.

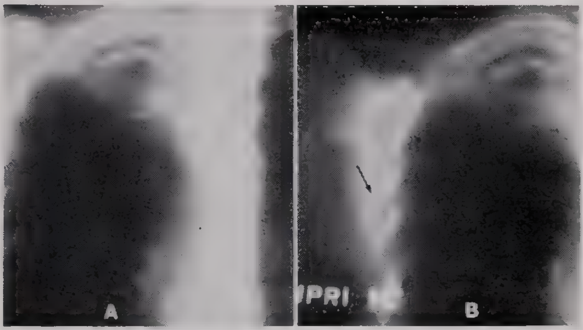

Fig. 6 — Intracavitary fungus ball. Section 8 cm. anterior to the table top. (a) Supine. (b) Erect. The fungus ball falls to the dependent inferior portion of the cavity when the patient is upright. Note the prominent "satellite shadows" (arrow).

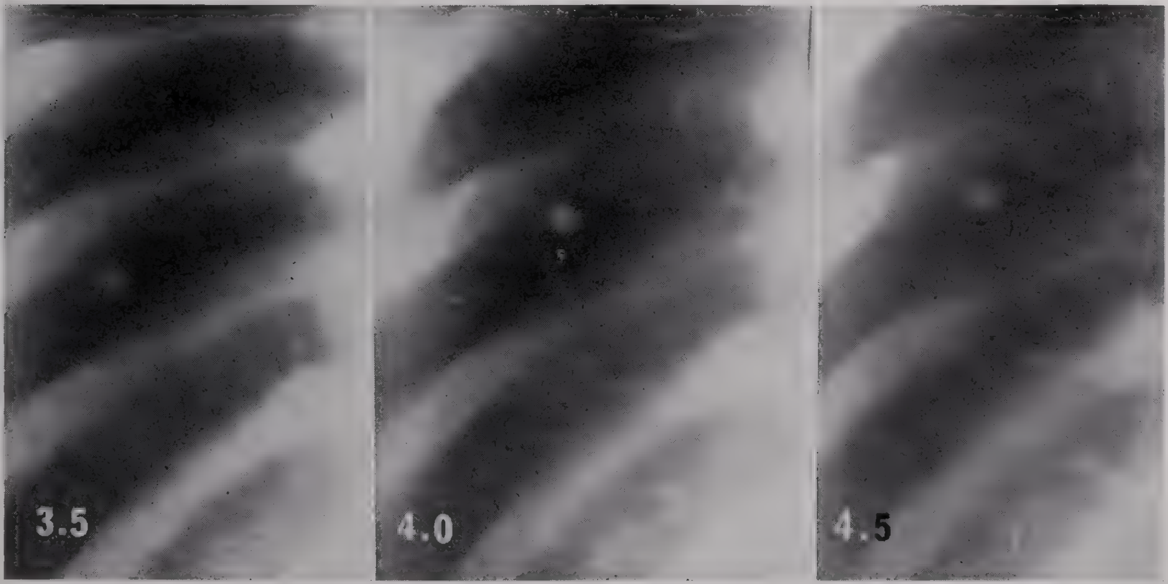

Fig. 4-b — Frontal AP tomograms made with hypocycloidal motion at 3.5, 4.0 and 4.5 cm. anterior to the table top. Maximal blurring of unwanted shadows was obtained and calcification was shown on the 4.0 cm. cut. Localization of the nodule for definitive study was difficult because of the thinness of the cuts.

The Mechanical Design

Stability

The Polytome is a very stable machine and thus is ideal for tomography. Stability of the unit is a great advantage over the tomographic attachments designed for use with regular radiographic equipment. Housing the Polytome in a room by itself is advisable. Tomographic examinations of the chest are frequently time-consuming and hence would often tie up a dual-purpose radiographic room. The "psychological block" to exploit fully the advantages of body section radiography disappears when adequate space is available exclusively for tomography. Of course, expense and overhead are greater in this circumstance.

The machine can be used with the patient in the erect or inclined position, whichever is advantageous in the delineation of cavitary disease and air-fluid levels (Figures 6 and 7).

Enlargement Technique

An additional cassette* holder is mounted below the normal cassette and grid holder which permits enlargement techniques. When coupled with a fine focus tube (.3 mm. focal spot) this apparatus produces detailed enlargements of 1.6 times. The routine tomograms enlarge 1.3 times. (The target-film distance and tomographic plane-film distance are always constant with this apparatus.)

The enlargement cassette holder can be tilted as much as 20 degrees from the horizontal. The geometry of tomography results in the plane of the section developing parallel to the plane of the film. Thus, inclined tomograms can be made. Several papers have appeared in the literature recently emphasizing the advantages of inclined tomography of the chest, especially to obtain visualization of the tracheobronchial tree and the pulmonary blood vessels. These results have been obtained by a fixed position of the tube with rotation of both patient and film. When using the Polytome, merely tilting the additional cassette holder produces inclined tomograms (Figure 8).

The first commercially available polytome would not permit routine radiographic examination because it lacked a conventional Potter-Bucky diaphragm. A new unit is available from Philips-Massiot which allows routine Bucky radiography in addition to Polytomography. However, this new unit cannot be used in the erect position.

Summary

The use of the Polytome in the respiratory tract has been reviewed. In the respiratory tract the full range of versatility of the

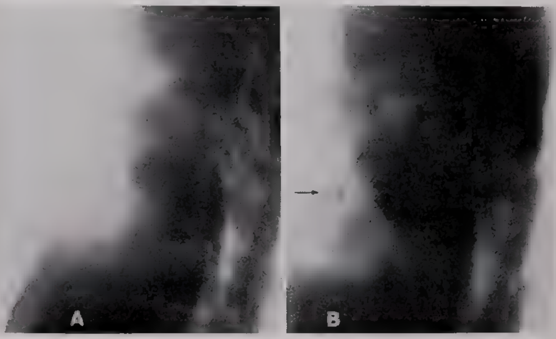

Fig. 7 — Pulmonary abscess cavity. Linear motion. (a) Supine 11.3 cm. anterior to the table top. A parenchymal density is seen without evident cavity. (b) Erect 11.0 cm. anterior to the table top. The air fluid level present indicates pulmonary cavitation (arrow). Tomography with the patient erect is invaluable to demonstrate cavitation.

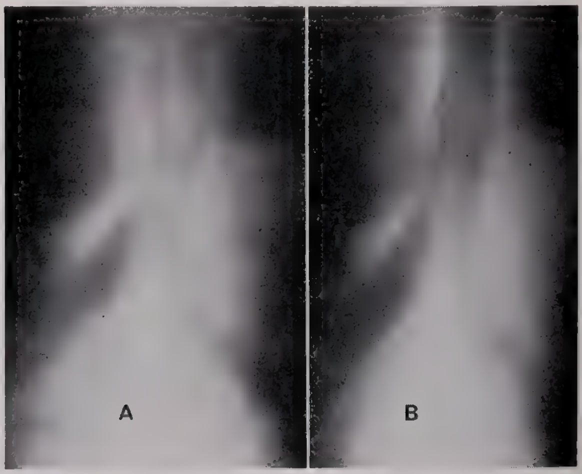

Fig. 8 — Tomography of the tracheobronchial tree. Hypocycloidal motion 11 cm. anterior to the table top. (a) Conventional AP tomogram. The film is parallel to the table top. The proximal trachea is not demonstrated. (b) Inclined AP tomogram. The cassette holder was tilted 15° to parallel the trachea. The entire plane of the trachea is in focus as is the plane of the carina and right and left main stem bronchi.

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*See Test Your Word Score Page 1855.

equipment can be exploited. Thorough knowledge of various technical considerations is mandatory to produce the best tomographic studies. When these factors are properly employed the resultant high quality tomograms add immeasurably to the roentgen evaluation of respiratory tract problems.

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IT'S THE LAW

Medical Texts Admissible Only to Test Expert Knowledge, Not to Prove Medical Theories

Medical books and treatises are not admissible to prove the truth of statements contained therein, the Supreme Court of Washington said. Moreover, even though such writings are admissible to test an expert witness' knowledge, their authoritativeness must first be proved if the witness refuses to concede it.

An article was introduced in a suit by a department store customer for injuries sustained on an escalator in the store. A doctor who testified as an expert witness was cross-examined on an article which appeared in the Journal of the American Medical Association, entitled "Survey of One Hundred Cases of Whiplash Injury after Settlement of Litigation." The article indicated that a substantial number of persons having whiplash injuries recovered after the termination of litigation.

In commenting on the article, the court declared that, "it seems to us no more entitled to be called a medical treatise than any other statistical study."

Even assuming the article to be a medical treatise, it was not admissible because it was not established as authoritative, and the doctor had not conceded it to be such. He had testified that he read the article, but he did not concede that he regarded it as other than a statistical study.

The court agreed that an expert should not be permitted to block cross-examination by refusing to concede that a text or treatise is authoritative. However, if he does refuse to concede that point, then the burden of proving that the text or treatise is authoritative is upon the cross-examiner. In this case, the burden was not sustained, the court concluded, since there was no evidence that the views expressed in the article were other than those of an individual doctor, based on a survey made by a senior medical student. Therefore, the jury should have been instructed to disregard that portion of the cross-examination relating to the article, either because it was not a medical treatise or, if it was a medical treatise, because it was not established to be authoritative.

Dabroe v. Rhodes Company, 392 P.2d 317 (Wash., May 14, 1964)

Science commits suicide when it adopts a creed. — T. H. Huxley

Moliere on Doctors

Dr. T.: Sir, we have been discussing your daughter's illness, and my own view is that it arises from overheating of the blood. My advice is therefore — bleeding as early as possible.

Dr. D.: In my opinion the trouble is a putrefaction of humours caused by a surfeit of er - er - something or other. My view is that she should be given an emetic.

Dr. T.: In my opinion an emetic would kill her.

Dr. D.: On the contrary, I maintain that to bleed her now would be fatal.

Dr. T.: You would try to be clever. Don't forget how you cooked that fellow's goose the other day.

Dr. D.: What about the woman *you* sent to glory only three days ago?

Dr. T.: If you don't have your daughter bled without delay, you can take it she's done for.

Dr. D.: If you *do* have her bled, she won't last a quarter of an hour.

Dr. F.: Aren't you ashamed, gentlemen, to show so little prudence? Men of your age quarreling like a lot of hot-headed boys! Do you not realize how such quarrels damage our reputation? If we are not careful we shall do ourselves irreparable harm. I am not concerned for myself, because, thank Heaven, I am now comfortably off. Come rain, come shine, dead men tell no tales, and I no longer need to rely on the living. But these disputes do Medicine no good. Since Heaven has so willed that all down the ages people should continue to put unquestioning trust in us, let us not risk disabusing them with these outrageous rivalries. Let us continue to profit from their gullibility so far as we can. After all, we aren't the only people who seek to make use of human frailty. Everyone endeavors to turn other people's foibles to his own advantage. . . . But of all human foibles love of living is the most powerful. And that is where *we* come in, with our pompous technical jargon, knowing as we do how to take advantage of the veneration which the fear of death gives to our profession. Let us therefore seek to preserve the high esteem with which human folly endows us. Let us maintain agreement in the presence of our patients. Thus we may take to ourselves the credit when their maladies end happily, and put the blame on nature when they don't. Let us not, I say, wantonly weaken that persistent delusion which fortunately provides so many of us with our daily bread and enables us, from the money of those we put under sod, to build a noble heritage — for ourselves.*

The above dialogue is a classic example of Moliere's inimitable satire: mischievous in tone — with just a touch of malice but with no trace of bitterness. In the farce L'Amour Medecin (Love's the Best Doctor) several physicians are called into consultation to diagnose the malady of a young woman suffering from nothing more than love-sickness. Throughout the comedy the medical profession is mercilessly scored: for its arrogance, pretentiousness, intransigence and authoritarianism. Moliere's doctors resent patients who recover from diseases diagnosed as incurable and likewise patients who die in the face of favorable prognoses. Such unorthodox outcomes constitute an affront to the corporate dignity and infallibility of the medical profession.

L'Amour Medecin was written in 1665 and was an immediate and hilarious stage success.

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*Moliere: Love's The Best Doctor: Translated from the French by John Wood.

Acute Arterial Occlusion in the Lower Extremity

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SUDDEN ARTERIAL occlusion urgently demands careful differential diagnosis and an accurate appraisal of the patient's total cardiovascular status in order to institute the proper treatment at the proper time. The prime problem in differential diagnosis is that of acute venous thrombosis. Here one may err in thinking the patient has an acute arterial occlusion when in fact he has acute venous occlusion with much arterial spasm. More often muscle ischemia secondary to acute arterial occlusion is mistakenly taken for the early signs of acute thrombophlebitis in the calf, and sometimes embolectomy is delayed so long that irreparable damage is done to the muscle.

Evaluation of the Patient

The present cardiac status of the patient must be assessed: (1) to estimate whether or not a poor cardiac output contributes to the peripheral ischemia; (2) to assess the patient's degree of cardiac compensation with particular reference to his ability to withstand anesthesia and the necessary surgical procedure to relieve arterial obtruction; and (3) to assess the total cardiac capacity of the patient in the future, because total cardiac capacity will determine whether or not one should settle for an extremity with claudication or whether one should go "all out" to restore circulation to normal.

Once the differential diagnosis is established between venous and arterial occlusion and the cardiac status is evaluated, then one must decide what the fate of the affected extremity is likely to be without surgical intervention, where the obstruction is, and (if the extremity is not likely to survive without surgery) what type of surgery is necessary to restore the circulation of the extremity to normal. The differentiation between acute arterial thrombosis and acute embolism becomes important, because in most instances embolectomy can be carried out under local anesthesia with minimal trauma, whereas acute arterial thrombosis in most instances will require general or spinal anesthesia and some type of grafting procedure.

We have had occasion to review the records at the University Hospital as well as others from our own personal experience in the past 13 years, and after critically analyzing the management of these patients by ourselves and others we have arrived at a plan of evaluation and management which we would like to present.

Differential Diagnosis

Acute arterial occlusion must be differentiated from acute venous thrombosis. Two illustrations will suffice to indicate the importance of this differential.

Venous Thrombosis with Arterial Spasm

The author was called by a surgeon in another city to consult. The patient was a physician's wife who three weeks before had developed what was thought to be a left lobar pneumonia. The day of the conversation the patient had developed a cold, numb, white, slightly swollen left lower extremity in which the surgeon was unable to feel the femoral pulse. He was concerned that the patient might have both acute venous thrombosis and acute arterial thrombosis. Upon our advice the patient was given 100 mg. of heparin by the intravenous route and transferred to our hospital. When she arrived four hours later the extremity was fairly warm; there was a good femoral pulse, and the extremity was more than two inches larger than the other, confirming the diagnosis of acute venous thrombosis with much arterial spasm. Review of the previous films and the previous history would indicate that she undoubtedly had suffered a pulmonary embolus three weeks previously and now had developed an acute obstructive iliac vein thrombosis.

Acute Arterial Embolus

The tender calf of acute muscle ischemia following acute embolization is unfortunately sometimes interpreted as a positive Homan's sign of deep venous thrombosis.

An elderly physician came into the hospital with what was thought to be a stroke from which he was recovering. He had had previous cardiac decompensation and had chronic atrial fibrillation. While he was in the hospital recovering from the "stroke", he developed pain and tenderness in the left calf. A medical resident made a note of this and said he thought the patient was developing acute phlebitis. The following morning he was seen by his attending physician who recognized that he had no pulse distal to the femoral, that this extremity was colder than the other and that the muscle power in this calf was deficient. Fortunately for this patient an embolectomy some 24 hours after the onset of his pain was still successful in restoring circulation to this extremity.

Ischemia — Diminished Cardiac Output

Occasionally one finds an ischemic extremity in which a poor cardiac output contributes markedly to the ischemia. When the cardiac output is improved the ischemia disappears. The cardiac output may be markedly diminished because of severe tachycardia or marked bradycardia.

While at a cattle auction a 78-year-old cattle buyer collapsed because of pain, numbness, and inability to use the left leg. When he was brought to the hospital he had very little motion in the calf of this extremity and absent vibratory sense in the foot. He had no femoral pulse on this side, but as one approached the aorta one noted that his pulse rate was actually 26. He gave no history of chest pain and the EKG showed only acute complete heartblock with idiopathic ventricular rhythm. On questioning the patient we learned that he had suffered from one block claudication for the previous year. Although our tentative diagnosis was embolic occlusion of the left common iliac artery there was some question about how much of the ischemia of this extremity was due to the severe bradycardia. At any rate, it seemed reasonable to raise his rate to near normal before contemplating even a local approach to the left common femoral vessels. While in the x-ray department having a temporary pacemaker implanted by the venous route, the ischemia of the extremity promptly disappeared as soon as the heart was paced at 70 beats per minute. The patient has now worn a permanent pacemaker for two years and has done very well without the necessity for any surgery on his extremities.

Extreme tachycardia may also contribute to the severe ischemia of the extremity. A 56-year-old woman underwent resection of an abdominal aortic aneurysm. At the conclusion of the procedure it was noted that she had no pulse in the left foot; but the motion of the extremity was quite satisfactory and she had a popliteal pulse. Undoubtedly she had some embolic material in the distal popliteal vessel, but we were sure that the extremity would survive. The following day the pulse rate suddenly rose to 180 due to a supraventricular tachycardia to which she has been subject in the past. With the onset of this severe tachycardia she developed severe pain in the left hip and the left calf, with inability to use either the anterior or posterior musculature of the calf. Following carotid pressure and restoration of the pulse rate to 100 all signs of ischemia of the extremity promptly disappeared.

Embolism vs. Arterial Thrombosis

The differentiation between acute embolism and acute arterial thrombosis is important because of the differing surgical approaches required. In almost all instances of acute arterial embolism, particularly with the advent of the use of the Fogarty[1] catheter, almost all emboli can be removed through a small incision under local anesthesia. An exception to this, of course, would be embolism to the superior mesenteric artery in the abdomen. The presence of acute arterial thrombosis which threatens the life of an extremity or the suspicion of acute arterial thrombosis demands more extensive procedures on the blood vessels than can practically be carried out under local anesthesia. How can one be sure that the acute arterial occlusion with which one is faced is an embolus or a thrombus? First, almost all peripheral arterial emboli come from the heart or from a palpable peripheral aneurysm. In our experience involving some 68 embolic episodes, in only three instances was there no good documented source for embolization: either from atrial fibrillation in rheumatic or arteriosclerotic heart disease; from mural thrombus due to a recent myocardial infarct; from some preceding cardiovascular procedure; or more rarely from a femoral or popliteal aneurysm. Not infrequently the patient who presents an acute peripheral arterial occlusion gives no clear-cut history of myocardial infarction; but this should be looked for in the absence of atrial fibrillation. An EKG and subsequent enzyme studies usually lead to such a diagnosis. The patient who has marked peripheral sclerosis in other parts of his vascular tree (e.g., upper extremity or carotids), is more apt to have arterial thrombosis than embolism, particularly in the absence of a good primary source, and in our experience the patient with other severe atherosclerosis may require a grafting bypass procedure even in the presence of acute embolization. So from the practical standpoint the patient who has atrial fibrillation or who has had a recent myocardial infarct with no other evidence of peripheral sclerosis except in the affected extremity has a better than a 90% chance of having a peripheral embolism which can be treated simply under local anesthesia. The patient who has other signs of peripheral sclerosis will usually require extensive vascular surgery which cannot be done under local anesthesia.

Prognosis of the Extremity

The fate of an extremity not treated by surgical means is all-important in making the surgical decision. In the past 13 years we have, on first examination, carefully evaluated every extremity in which acute arterial occlusion has occurred, in order to project the fate of this extremity if unoperated. In the early part of this period some patients whose extremities seemed potentially not viable by our criteria were subjected to sympathetic blocks and some to heparin administration. In no instance, following either of these two modalities of therapy have we seen a reversal of impending gangrene which could be attributed to these methods of treatment.

With no therapy, we have seen spontaneous and dramatic improvement of an extremity which has had all the criteria portending gangrene. In these instances we postulate that an embolus which had lodged in the bifurcation had broken up into smaller particles and gone down into the muscular branches, leaving the main channel open.

Sympathetic Block and Heparin

It is true that in many instances an extremity which we would regard as survivable improves following a sympathetic block and also following heparin administration. In such instances where surgery is not absolutely necessary, either of these modalities of therapy would seem to be indicated to prevent thrombosis of smaller vessels. We have had no experience with low molecular Dextran in these instances.

Impending Gangrene

Following a critical analysis of all the case records, we have come to the conclusion that the status of the muscle in the extremity is the single most important prognostic factor. If the muscle is paralyzed and hard, rigor mortis has set in and no revascularization is possible. If the muscle is tender and still soft, with motor power diminished or absent, and if proprioception* is impaired, then this muscle in our opinion is suffering from severe ischemia but is still salvageable if the obstruction to the supplying artery is relieved. If motor power is completely gone, the blood supply has been effectively cut off. If motor power is merely impaired, there is less ischemia of the muscle. Tenderness is usually confirmatory evidence of ischemia. Proprioception or position sense is also related to the blood supply of the muscle. We have noted that often the skin seems to be intact when the muscle has already become infarcted. These criteria, we are sure, apply very specifically to all patients with acute embolism.

Surgery Indications and Contraindications

Given a patient with acute peripheral embolism the decision for or against surgical intervention depends upon (1) the projected fate of the extremity, and (2) the recoverability of the heart. If the patient has thrown an embolus from the atrium in the case of mitral stenosis which is correctable, then certainly the embolus should be removed even if the extremity would survive without surgical intervention. On the other hand, a patient who has suffered a severe massive myocardial infarct which had thrown off a peripheral embolus that was not threatening the extremity would hardly be a surgical candidate in order to cut down the possibility of future claudication. The occurrence of a peripheral embolus which is producing sufficient ischemia to threaten the life of the extremity is, in our opinion, a clear-cut indication for removal of the embolus even in the presence of moderate degrees of cardiac decompensation, for surely necessary amputation in such a patient carries a high mortality.

TABLE I
Arterial Embolectomy

Location	Number of Emboli	Number Survived
Aorta	13	7
Iliac	7	7
Common Femoral	18	15
Superficial Femoral	10	7
Popliteal	16	15
Upper Extremity	4	3
	68	44

TABLE 2
Results by Etiology

Etiology	Patients	Patients Survived
Myocardial Infarction	14*	9
ASHD with Fib.	23	19
Rheumatic Heart Dis.	9	9
Cardiovascular Procedures	9	7
	55	44

*Graft in 1 case.

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*See Test Your Word Score Page 1855.

The distribution of emboli according to location is about the same in our series as in those others reported in the literature and needs no comment.

It should be noted that the great proportion of patients have arteriosclerotic heart disease, but there is also a very high proportion of fresh myocardial infarcts.

Treatment

Early Operation

Embolectomy is very successful in restoring the circulation to normal if done early; but unfortunately it does not always correct the primary cause of the embolization. In the past three years, we have had occasion to operate on 21 patients for acute embolism. In 19 of these simple embolectomy was carried out and in two some grafting bypass procedure was judged necessary. In this period six patients had emboli above the inguinal ligament either aortic or iliac. Three were operated on under local anesthesia and all underwent exploration from below without opening the abdomen. Unfortunately, in this group there were three deaths, two of them of cardiac failure following coronary thrombosis, and one probably from an overlooked mesenteric occlusion. In the three survivors all extremities were normal. There were 15 patients who had emboli lodging below the inguinal ligament; in 11 of these a Fogarty catheter was used and in two a grafting procedure was necessary. Ten patients were operated on within 12 hours of the onset with no resulting peripheral ischemia. However, two of these died of other emboli to the brain.

Late Operation

Five patients were operated on after more than 12 hours; in this group only one patient did not require an amputation. One of these patients died of a cerebral embolus. In our total group of emboli seen in the past 13 years there have been 28 patients operated on who in the judgment of the operating surgeon had such severe muscle ischemia that gangrene would have ensued had they not had surgical intervention. In this group gangrene of the extremity occurred in only one patient, undoubtedly because an embolus in the popliteal artery was overlooked.

Local Anesthesia

The importance of local anesthesia for embolectomy wherever possible should be emphasized, not only because of its relative safety but because as soon as the arteriotomy is closed and the blood allowed to go down into the extremity the success of the procedure is immediately demonstrable by the motion of the muscle previously motionless. Localization of the embolus can usually be made by palpation in order to make the incision in the proper place. If the embolus lodges above the inguinal ligament and there are no femoral pulses and no signs suggestive of bowel ischemia, one can make bilateral femoral arteriotomies under local anesthesia. If the embolus lies below the inguinal ligament one can usually palpate the superficial femoral artery down to the point of occlusion. If this is not conclusive, then the point of occlusion can be quite simply picked up within a few centimeters by the use of an oscillometer.

Acute Arterial Thrombosis

Unfortunately our experience with acute arterial thrombosis has not been as happy as with peripheral emboli. An extremity may seem to be potentially viable today; tomorrow it may be much worse. Three case histories will indicate the problems of management.

Case 1.

A 77-year-old round-back male was admitted to the University Hospital with a sudden onset of coldness and with numbness of his left foot which had been present for four hours. On examination, sensation of the skin was absent up to the ankle; the second and third toes were dusky blue; there was still plantar flexion and dorsiflexion of the foot but absent proprioception in the great toe. In the course of the workup in the next two hours the chest film showed unequivocal evidence of carcinoma of the left lung. The presence of this obviously inoperable carcinoma in this particular patient made us pause overnight to decide whether or not to do anything for this extremity. The next day the second toe was definitely gangrenous, and it seemed obvious that the patient would soon lose his extremity if something were not done to correct the advancing gangrene. We therefore explored the left popliteal artery under general anesthesia and found it to be patent and soft, injected it with dye and discovered the runoff to be adequate. . . . We then put in a stretch dacron prosthesis from the common femoral to the distal popliteal, which functioned so satisfactorily that he was able to walk upon this leg for about eight months until forced to go to bed for the terminal stages of his bronchogenic carcinoma.

Case 2.

A 68-year-old female two years previously had suffered a right hemiplegia which left her with a residual spastic gait in her affected lower extremity but with return of speech and use of her upper extremities. About 18 hours prior to admission to the hospital she had developed pain and numbness of the right lower extremity with progressively increasing inability to move the musculature in her calf, anesthesia to the lower calf, and loss of proprioception. It appeared that gangrene would soon ensue, although the extremity at this time seemed to be potentially still viable. In view of the spastic situation in this extremity, however, it seemed unlikely that she would be able to handle a prosthesis. She was taken to the operating room and fortunately a graftable situation was found. A dacron prosthesis was placed between the common femoral and the distal popliteal, and since this graft was inserted she has been walking as well as before.

Case 3.

This elderly lady of 78 was in the hospital for a vein stripping of the left leg. The fifth day afterward she developed pain and numbness in the right lower extremity below the knee, with tenderness in the anterior tibial compartment. One could palpate the common femoral artery and superficial femoral artery down to the distal third of the thigh. The wrong clinical impression was then entertained by the author; he thought that the extremity was irretrievable and probably not reconstructable. An arteriogram done the following day showed to our surprise that the distal popliteal artery and all three of its branches were open. We then carried a saphenous vein graft from the common femoral to the distal popliteal, which has functioned now for more than a year with palpable dorsalis pedis pulse. However, delay had resulted in ischemia of the entire anterior tibial compartment of the muscle, which of necessity had to be removed. The defect was covered with a skin graft which necessitated hospitalization for about two months. The patient, however, is walking on this extremity, and although deformed it is probably better than an artificial limb.

Arteriography

We have used arteriography very infrequently in patients with acute arterial occlusions. The diagnosis and localization of peripheral emboli can usually be quite satisfactorily made on clinical grounds. Occasionally in a borderline case an arteriogram will show definitely by its configuration that the occluding matter is embolic rather than thrombotic. However, I think a word of caution is necessary in interpretation of arteriography with acute arterial thrombosis. It has been our experience that an arteriogram may show no peripheral runoff in the presence of acute arterial occlusion because there is simply not enough blood carrying the dye into the distal segment past the occluding thrombus. In general our approach to acute arterial thrombosis is that, if we are confident that the extremity will not survive without surgical intervention, we explore the distal popliteal artery directly. If the main trunk of the artery is open we usually inject iodine-containing dye to determine the patency of the distal tree. If this is patent then we go ahead with the grafting procedure. If the popliteal is occluded, then hopefully we gain permission for amputation.

Conclusion

We have pointed out the importance and the means of differential diagnosis between acute arterial thrombosis and acute peripheral embolism, indicating that emboli can be removed under local anesthesia by the standard simplified technique but that arterial thrombosis requires much more extended procedures requiring spinal or general anesthesia. A strong plea has been made for the accurate appraisal of the potential fate of the extremity at the time of the initial examination. Medical measures are advocated only in those extremities or for those patients whose extremities will almost surely survive without surgical intervention. It was pointed out that early embolectomy with occasional use of graft is almost always successful in preventing gangrene of the extremity. Acute arterial thrombosis has been shown to be a very insidious and difficult problem to handle; but an aggressive approach has resulted in the saving of some extremities which otherwise would have been lost.

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Treatment of Rheumatoid Arthritis

Chemical and Surgical Synovectomy

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RHEUMATOID ARTHRITIS may be defined as a chronic inflammatory disease characterized by proliferative and destructive changes in joints leading to ankylosis and deformity. Galen[1] first used the word rheumatism in the first century A.D. However, no clear-cut classification of arthritis was made until Gerrod[1] in 1859 differentiated between osteoarthritis and rheumatoid arthritis. Nicholas and Richardson[1] first stated that in rheumatoid arthritis there are proliferative changes in joints, chiefly in the synovial lining, while in osteoarthritis the changes arise as a degeneration of cartilage.

Manifestations of Rheumatoid Arthritis

In the earliest stages of rheumatoid arthritis the disease is a synovitis, characterized by synovial hyperemia, edema, and increase in joint fluid. The synovialis may increase from a single-layer thickness to a great many cell layers. Synovial villi enlarge and hypertrophy.

The most significant and serious manifestation of rheumatoid arthritis is the pannus* formation over the articular surfaces. Pannus originates in the part of the synovial membrane bordering the articular cartilage and first appears as tongues of granulation tissue creeping from the periphery toward the center of the joint, producing destruction of cartilage.

Types of Treatment

The cause of rheumatoid arthritis is as yet unclear. While research for a specific etiology is in progress, attempts at treatment by non-specific therapy have been numerous. The materials used by the medical profession for this purpose through the years have been legion; among the most popular have been typhoid bacillus, a shotgun mixture of streptococcus and staphylococcus, colloidal sulphur, casein, colloidal gold, aspirin, butazolidin, steroids, and the antimalarials. Because rheumatoid arthritis is a disease of hyperplastic synovium, a more direct attack would seem to be based directly upon removal of the tissue.

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*See Test Your Word Score Page 1855.

Chemical Synovectomy

A method of treatment which would remove the hypertrophic synovium completely and not subject the patient to an extensive surgical procedure and long convalescent period would be ideal. A chemical synovectomy with a nontoxic, cartilage-sparing, easily-injectable substance would certainly have many advantages over surgery. Such a chemical synovectomy has been attempted by the intra-articular use of nitrogen mustard and thiotepa. These substances are alkylating agents well known in the treatment of metastatic tumors. In contrast to thiotepa, nitrogen mustard is a local vesicant, contact with which can lead to a serious local reaction. Because of this feature of the drug we have concentrated our attention on the use of thiotepa.

Thiotepa is thought to act on the desoxyribose nucleic acid molecule of the rapidly developing cells of the hypertrophic synovium to prevent cell multiplication.

Alkylating agents have been used in the treatment of rheumatoid arthritis since 1951 when Diaz[2] reported using nitrogen mustard systemically in nine severe cases of arthritis with rapid relief of pain. Scherbel[3] and Scherbel, Schuchter, and Weyman[4] in 1957 published extensive experiences with nitrogen mustard in animal and clinical trials in which the drug had been administered via both the intra-articular and parenteral routes. In one group of 263 patients Scherbel[3] reported 88 percent rapid relief of symptoms but with recurrence of symptoms in all cases. Vainio and Julkunen[5] of Finland injected symmetrical joints with 25 milligrams of hydrocortisone and 0.5 milligrams of nitrogen mustard. Although the symptoms reappeared in each case, the mean extent of time of remission was 2.3 months. We have a small series of five patients in whom we have injected thiotepa into the involved joints. In all instances but one there was a rapid and dramatic relief of joint pain within 48 hours, followed by marked regression in synovial thickening. In each case there was a recurrence of synovial thickening and fluid within six months. In one patient patellectomy was performed six weeks after 60 milligrams of thiotepa was instilled

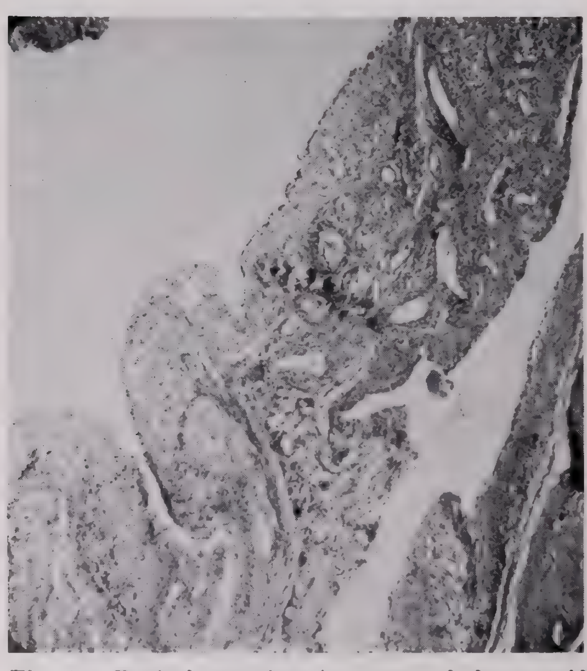

Fig. 1 — Typical synovium in a case of rheumatoid arthritis.

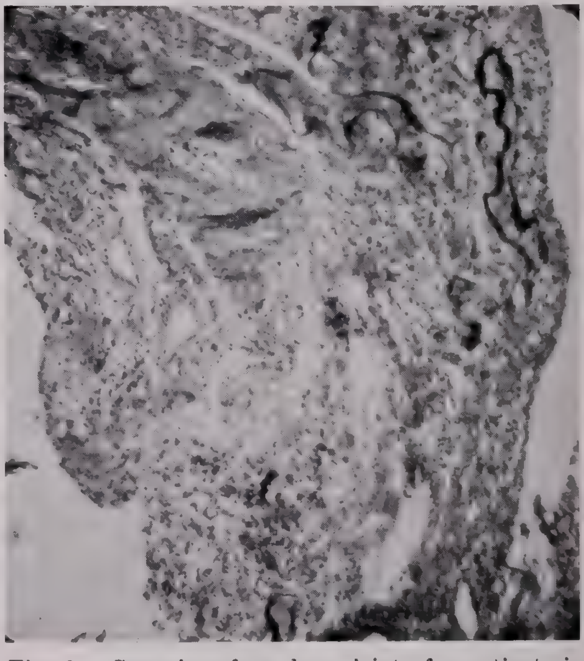

Fig. 2 — Synovium from knee joint of a patient six weeks after the injection of thiotepa into the joint. Note the marked fibrinoid necrosis.

into the knee joint. The synovium at the time of arthrotomy was reddish grey in color and not thickened. Microscopic examination revealed marked fibrinoid necrosis of the joint lining (Figure 2).

Surgical Synovectomy

Although the alkylating agents produce rapid remissions in rheumatoid arthritis, it appears that recurrences in the same joint are inevitable. Because of this observation we have abandoned chemical synovectomy in favor of surgical synovectomy. We believe that synovectomy is a worthwhile surgical procedure for the rheumatoid knee joint and for the metacarpophalangeal joints of the hand. The ideal joint for surgery is one with persistent chronic arthritis which has not improved with conservative treatment. The surgery should be undertaken before there is extensive joint and ligamentous destruction. Although the best results might be expected in patients whose articular cartilage has not yet been invaded, satisfactory results have been achieved in patients with moderately advanced joint destruction.

Results of Surgical Synovectomy

Aidem and Baker[6] reported on using synovectomy in 26 rheumatoid knee joints with 11 excellent, 12 good, one fair, and two poor results. Even in the group with fair and poor results there was no recurrence of the preoperatively swollen, boggy knee. We have performed synovectomy in 13 rheumatoid knees with eight excellent, two good, one fair, and two poor results.

Timing of Operation

The timing for surgical intervention is critical. We do not feel that synovectomy is indicated in the face of acute generalized arthritis. In such cases we employ systemic medical treatment and physiotherapy awaiting the cessation of the generalized activity to then treat the chronically involved joints. Preoperative physiotherapy stressing efforts to achieve full extension is extremely important. Preoperative splinting is indicated in patients who cannot otherwise attain full extension of the knee. Active exercises are encouraged. Often intra-articular steroids will reduce joint pain enough to improve knee motion.

Resumption of Motion

Early resumption of joint motion postoperatively is important. We encourage joint motion 72 hours following surgery. If the patient does not have a 90-degree range of motion in the knee within 10 days, we gently manipulate the joint under general anesthesia.

Conclusions

Rheumatoid arthritis is at present a discouraging disease to treat. It is unpredictable and often produces severe bone and joint destruction and total invalidism. Or it may spontaneously subside. We feel that in the patient who has chronic arthritis, rather than allow the condition to progress to produce severe joint deformity, an aggressive surgical attack on the wayward synovium is beneficial. Chemical synovectomy produces only a temporary remission. Further conclusions regarding chemical and surgical synovectomy in the treatment of rheumatoid joints await long-term studies involving large numbers of patients.

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Madness

Madness is to think of too many things in succession too fast, or of one thing too exclusively. — Voltaire

Disease and Music

Tarantism

Endemic to the province of Apulia on the east coast of the Italian heel during the medieval era and epidemic throughout the scorching summer season was an exotic and baffling disease: tarantism. Its victims were called tarantists; its cause was the tarantula; and its only cure was the tarantella.

According to descriptions by reliable observers, Ferdinandus, a physician, Baglivi, an iatromechanist, and Kircher, a Jesuit father, the victims of the disease, immediately after being bitten by the 'deadly' spider, rushed out to the public street or market place and commenced dancing in a frenzy — with unmistakable and provocative overtones of alcoholic and aphrodisiac abandon.

The only remedy for the dance delirium was music, the wild and passionate tarantella, usually furnished by roving bands of musicians who proceeded from town to town capitalizing on the bizarre hysteria the summer's heat produced. To the tarantella the tarantists danced orgiastically until, too exhausted to continue, they stopped — supposedly cured. However, because of its insidious nature the disease abated only temporarily — to be reactivated by the heat of succeeding summers. Its incidence was highest among young people, though records show that a boy of five and a man of ninety-four once succumbed.

Naturally, doctors were dubious. One sceptical physician allowed himself to be bitten twice by the spider. His arm swelled up but no irresistible compulsion to dance seized him. Therefore it could not be the tarantula that caused the terpsichorean obsession. Then what? A mysterious neurosis, the doctors theorized. But then — whence came it? No one could explain!

However, like the Roman Empire itself, tarantism rose and fell — its etiology remaining obscure to the last. Only much later did historical perspective provide a clue to the enigma. The early natives of Apulia had been special devotees of the pagan cult of Dionysus with its orgiastic alcoholic and sexual rites. But the Church had peremptorily stopped all such demonstrations. Nevertheless, while Dionysian practices might be summarily prohibited, the urge to indulge in those practices could not be arbitrarily repressed. So the people continued to dance in the searing heat of the Apulian summers. Compelled to repudiate the traditional excuse for their annual extravagant orgies they simply substituted a socially more acceptable reason: the tarantula's bite — an act of God which did not fall within the Church's province.

The Difference

We must bear in mind the difference between thoroughness and efficiency. Thoroughness gathers all the facts, but efficiency distinguishes the two-cent pieces of non-essential data from the twenty-dollar gold pieces of fundamental fact. — William Mayo

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A man may dwell so long upon a thought that it may take him prisoner.

— Halifax

Editorials

An Architect of Medical Education

ANY REVIEW of the impact of the University of Minnesota on the Upstate Medical Center of the State University of New York would be incomplete without some recognition of the unique contributions of an alumnus of the University who did not graduate from its medical school — Dr. Carlyle F. Jacobsen (Ph.D. in psychology, 1928).

Among the many Minnesota alumni who have made distinguished contributions to medical education, it is fair to say that Dr.

Dr. Carlyle F. Jacobsen, President
State University of New York, Upstate Medical Center

Continued

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Formulas: Each 'Dexamyl' Spansule® capsule (brand of sustained release capsule) No. 1 contains 10 mg. of Dexedrine® (brand of dextroamphetamine sulfate) and 1 gr. of amobarbital, derivative of barbituric acid [Warning, may be habit forming]. Each 'Dexamyl' *Spansule* capsule No. 2 contains 15 mg. of Dexedrine (brand of dextroamphetamine sulfate) and 1½ gr. of amobarbital [Warning, may be habit forming].

The following is a brief precautionary statement. Before prescribing, the physician should be familiar with the complete prescribing information in SK&F literature or *PDR*.

Precautions: Use with caution in patients hypersensitive to sympathomimetics or barbiturates and in coronary or cardiovascular disease or severe hypertension. Do not use in patients taking MAO inhibitors. Excessive use of the amphetamines by unstable individuals may result in a psychological dependence; in these instances, withdraw the medication. Use cautiously in pregnant patients, especially in the first trimester. *Side effects:* Insomnia, excitability and increased motor activity are infrequent and ordinarily mild.

SK&F SMITH KLINE & FRENCH LABORATORIES

Jacobsen ranks in the top group. His contributions extend far beyond the confines of this Center.

Perhaps the pervasive characteristics of Dr. Jacobsen's diversified career contributions have been those of architect, planner, and builder. These attributes were evident early in his scientific work. Following his graduation from the University of Minnesota his design and planning abilities were devoted to the development of novel learning tests for primates. He went on to work with the distinguished physiological psychologist Lashley at Chicago where he began his classic studies on the functional architecture of the cerebral cortex. This work was continued and extended by joining the late Professor John F. Fulton's group in neurophysiology at Yale during its halcyon* period of the thirties. This work formed some of the basis for the neuropsychology which has developed lately (on a recent visit to the Soviet Union it was found that the workers in the primate laboratory at the Pavlovian Institute were thoroughly familiar with "Jacobsen's work.")

It was reasonable to expect, therefore, that when Dr. John Whitehorn went to Washington University in St. Louis in the late thirties to develop a department of psychiatry, one of his first appointments would be Carlyle Jacobsen as professor of medical psychology. In addition to his teaching and research assignments his psychological background was applied to the problems of medical school selection, and through his talents for design he subsequently became one of the architects of the Medical College Admissions Test. His planning abilities were recognized more and more, and with the coming of World War II he was increasingly involved in medical school and university administration. In 1946 he accepted an invitation from the University of Iowa to become a Dean of the Graduate School and later assumed the post of Executive Dean of the Division of Health Sciences and Services.

But perhaps his greatest contributions to medical and to higher education have been made since he joined the State University of New York. In 1950, just after the State University had been established (in a State which had a tradition of strong private universities and no state university — something difficult for a mid-westerner to fathom), Dr. Jacobsen's appointment to the central staff of the new State University as Executive Dean for Medical Education was indeed fortunate. For in addition to his personal capacities, his background in two strong state universities and two private universities provided an appropriate blend from which to begin to plan. Because of his widely ranging interests and his presence in the central office of the University, his influence was felt on the development of the total University and not exclusively on that of the Medical Centers. The continued growth of the University is in no small measure a reflection of his influence on the early evolution of the educational policy and program.

By 1957 the development of the Downstate and Upstate Medical Centers under Dr. Jacobsen's jurisdiction had progressed to the point where greater autonomy for each of the Centers (and other units in the University) seemed desirable, and the position of Executive Dean was therefore eliminated. Dr. Jacobsen continued his leadership as President and Dean of the Upstate Medical Center from 1957 to 1965; in 1965 he relinquished the deanship in order to devote his full attention to the expanding responsibilities of the President's office.

From the accomplishments at the Upstate Medical Center the diversified talents of Dr. Jacobsen as educator, administrator, and builder are most apparent. The period under his leadership has been one of rapid growth of physical plant, of educational programs, and of faculty strength. The number of medical school graduates has approximately doubled, and his interest in the allied health professions has been manifested in an increased graduate student enrollment and the establishment of innovative educational programs in nursing, medical technology, and x-ray technology. The educational bud-

Continued

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*See Test Your Word Score Page 1855.

Frankly, most antihypertensives are pretty good if you give an adequate dose. I'm looking for one with a simple regimen so that mix-ups in doses and therefore the chance of side effects are minimized.

Regroton®

chlorthalidone 50 mg. reserpine 0.25 mg.

1 tablet daily
brings pressure down

Advantage: Both components of Regroton are long-acting.
Average dosage: One tablet daily with breakfast.
Contraindications: History of mental depression, hypersensitivity, and most cases of severe renal or hepatic diseases.
Warning: Discontinue 2 weeks before general anesthesia, 1 week before electroshock therapy, and if depression or peptic ulcer occurs. With administration of enteric-coated potassium supplements, the possibility of small bowel lesions should be kept in mind.
Precautions: Reduce dosage of concomitant antihypertensive agents by one-half. Discontinue if the BUN rises or liver dysfunction is aggravated. Electrolyte imbalance and potassium depletion may occur; take particular care in cirrhosis or severe ischemic heart disease and in patients receiving corticosteroids, ACTH, or digitalis. Salt restriction is not recommended. Use with caution in patients with ulcerative colitis, gallstones, or bronchial asthma.
Side effects: Nausea, vomiting, diarrhea, muscle cramps, headaches and dizziness. Potential side effects include angina pectoris, anxiety, depression, drowsiness, hyperglycemia, hyperuricemia, lassitude, leukopenia, nasal stuffiness, nightmare, purpura, urticaria, and weakness.
For full details, see the complete prescribing information.
Availability: Bottles of 100 and 1000 tablets.

Geigy

get has increased approximately ten-fold. Cardinal to this rapid development has been the recruitment of a faculty with a wholesome balance among investigative, teaching, and patient-care responsibilities.

The physical plant has been expanded to meet the increasing demands of the educational, research, and service programs. In 1957 an addition to the basic science building more than doubled the space for the basic science departments. In July 1964, a new outpatient wing of the new teaching and research hospital was opened; in July 1965, the 360-bed University Hospital (at a cost of approximately 25 million dollars), including new research laboratories for the clinical departments of the faculty, was opened. Two new student dormitories have been added to the Center's complex, and ground was broken this summer for a Student Activities Building.

On the national scene Dr. Jacobsen's counsel has been sought by foundations and public agencies. He served as Executive Vice Chairman of the Ford Foundation's Medical School Grants Committee as well as on the Surgeon General's Committee on Medical School Grants and Finances. He also served the National Foundation for Infantile Paralysis in various capacities from 1949 to 1961. His role as an innovator was recognized by the National Institutes of Health by his appointment to the initial National Advisory Council on Health Research Facilities and subsequently to the initial National Advisory Council on the General Medical Sciences. He has served on National Research Council Committees and on various committees of the Association of American Medical Colleges. He acted as co-chairman of the AAMC Teaching Institute on Medical Services and Medical Education — Today and Tomorrow. He is frequently consulted by various agencies and institutions for guidance in meeting needs in health manpower.

We could go on elaborating the accomplishments of a psychologist who has served as one of the architects of modern medical education. But in a sense it would be carrying coals to Newcastle, for the University of Minnesota has already bestowed on Carlyle F. Jacobsen its Outstanding Achievement Medal.

Julius B. Richmond, M.D.
Dean, The Medical Faculty
State University of New York
Upstate Medical Center

New York Upstate Medical Center

MINNESOTA MEDICINE is privileged to publish in this issue a group of articles from the Upstate Medical Center of Syracuse, New York. Dr. Julius Richmond, Dean of the Medical School, pays tribute to the University of Minnesota, the Alma Mater of Dr. Carlyle F. Jacobsen, President of the State University of New York, Upstate Medical Center in Syracuse. The University of Minnesota, he points out, has already paid its tribute to Dr. Jacobsen by awarding him its Outstanding Achievement Medal in 1951.

Minnesota physicians will take vicarious pride in reading of the career of this Minnesota psychologist, a career which includes the deanship of a great medical school.

Another former Minnesotan contributing to this "Upstate Medical Center" issue of MINNESOTA MEDICINE is Gordon Moe, M.D., Ph.D. in physiology, University of Minnesota, 1940. Many Minnesotans will recall that in 1958 Dr. Moe was also given the University of Minnesota's Outstanding Achievement Award.

Syracuse, like Minnesota, is the beneficiary of Masonic support of medical research.

MINNESOTA MEDICINE welcomes contributions from other states as single articles of general medical interest, as symposia, or as in this issue, a group of articles from an outstanding institution. We thank the contributors from Syracuse, and say to them, misquoting Shakespeare: "Physicians of Syracusa say no more; it hath in solemn synods been decreed, both by Syracusians and ourselves to honour each the other in our adverse towns."

Reuben Berman, M.D.
Minneapolis, Minnesota

SQUIBB NOTES ON THERAPY

Breast-feeding and the "modern mother"

Despite a mild resurgence of interest in the importance of breast-feeding a few years ago, many women today do not choose to nurse their young. This is for a variety of reasons—social, economic, cultural and sometimes medical. In such cases the physician's task is to find the most suitable means of preventing lactation and easing the pain of breast engorgement.

The means of therapy

The value of hormone therapy for this indication is of course well established. Both androgen and estrogen are known to inhibit the production and secretion of the lactogenic hormone by the anterior pituitary. As estrogen levels decline sharply at parturition, lactogenesis is established. When androgen and estrogen are administered to the patient before the release of the lactogenic hormone lactation and breast engorgement are usually prevented.

The time of therapy

The time of administration of this combined medication is crucial; it must be given early enough to suppress the pituitary prolactin and last long enough to permit physiologic readjustment during the puerperium. Excellent results are most often seen when therapy is administered before the onset of the second stage of labor.

However, factors other than effectiveness must also be considered. The agent selected should not interfere in any way with parturition, subsequent uterine involution and the restoration of normal ovarian cyclic function. Furthermore, it should not cause rebound breast engorgement or other manifestations of hormonal imbalance.

A balanced formulation

Providing single-dose therapy for the prevention of lactation and breast engorgement, Deladumone OB is a potent androgen-estrogen combination with a prolonged action. The optimal balance of androgenic and estrogenic hormones achieved in this preparation minimizes the disadvantages inherent in single hormone therapy, such as rebound breast engorgement. Involution of the uterus and resumption of menstrual cycles are not affected.

As reported in a recent published study (Roser, D. M.: Obstet. & Gynec. *27*:73, 1966), Deladumone OB provided good suppression of breast engorgement in 95.3% and suppression of lactation in 81.1% of 86 obstetrical patients. These results are in general agreement with those of many earlier investigations; in several studies this injectable androgen-estrogen combination proved to be superior to oral medication.

Dosage:

As a single injection of 2 cc. before the onset of the second stage of labor.

Contraindications:

Established or suspected mammary cancer or genital malignancy.

Precautions and Side Effects:

Certain patients may be unusually responsive to either estrogenic or androgenic therapy. In such individuals virilization, uterine bleeding or mastodynia may occur.

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Deladumone OB, providing 180 mg. testosterone enanthate and 8 mg. estradiol valerate per cc., is available in 2 cc. Unimatic® disposable syringes and in 2 cc. vials. Both preparations are dissolved in sesame oil, with 2% benzyl alcohol as a preservative. *Before use, consult product literature for full prescribing information.*

Deladumone® OB

Squibb Testosterone Enanthate (180 mg./cc.)
and Estradiol Valerate (8 mg./cc.)
Single-dose injection for lactation inhibition

SQUIBB *'The Priceless Ingredient' of every product is the honor and integrity of its maker.*

What Are We Doing in This Joint?

THE SURGERY of arthritis is the surgery of joints. Any surgeon who approaches the problem must accept the fact that rheumatoid arthritis in particular is primarily a generalized disease involving connective tissue and that joint impairment is a secondary manifestation. However, it is the joint symptoms that bring the patient to the physician and it is the joints that offer themselves for palliative or corrective procedures.

"To bend or not to bend" is a recurring question when considering the surgical approach to an arthritic joint. Such joints were made to bend originally and the ideal is to restore a damaged articulation as nearly as possible to normal. But the original models were also made to bend painlessly in a predictable direction and to provide a stable fulcrum over which the muscles could work. Can these features be restored?

As with the rest of medicine there is no perfect solution, but in individual cases there is usually an acceptable compromise. In the past the tendency has been toward arthrodesis to eliminate pain and provide stability. The list of authors and techniques for fusing each joint is long and reads like a "Who's Who" of orthopedic surgery. Emphasis has tended to shift gradually toward arthroplasty with the aim being to reduce pain while maintaining or restoring motion and preserving stability. This has been attacked with creative ingenuity and an astonishing supply of metallic gadgetry, with substantial but not uniform success. Failures at this stage have prompted a more aggressive approach advocating surgical intervention before the joint begins to lose the basic components of function. Synovectomy, osteotomy for joint realignment, tendon reposition or transfer — all have been designed to minimize or delay joint deterioration. In these cases the surgeon must derive his satisfaction from a technical job well done and a conviction that his patient will be spared future trouble. The patient himself is rarely exuberant when he is persuaded to undergo an operation before symptoms make it an obvious necessity.

There is no operation yet devised which can completely prevent progression of disease or return a destroyed joint to a normal condition. The primary goal is usually prevention of pain or pain relief; but in the case of multiple major joint involvement, maintenance of motion may be an overriding consideration. Where to start and when to stop are frequently imposing problems when dealing with the rheumatoid arthritic: the first often determined by the surgeon's fancy, the second by the patient's endurance. At best surgery is only a partial answer; but as increased understanding of the mechanisms behind arthritis should begin to eliminate the crippling end result, so should improved knowledge of the physiology and mechanics of articulations eventually make it possible to approach the devastated joint with a confident appraisal of "what we are doing there."

David G. Murray, M.D.*
Syracuse, New York

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*Associate Professor and Chairman, Department of Orthopedic Surgery, Upstate Medical Center.

Phrenic Nerve at the Esophageal Hiatus

AS DOCOTORS KLETSCHKA and Wynyard* have pointed out, the finer details of the distribution of the phrenic nerves to the diaphragmatic musculature have received scant consideration in the commonly used anatomical texts. This applies especially to the terminal distribution of the posterior divisions of the phrenic nerves as they course on and in the substance of the crura adjacent to the esophageal hiatus.

Continued

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*See page 1821.

when agitation

accompanies

spasm of the

'G. I.' tract.

Butadonna®

BUTABARBITAL SODIUM 15 MG. (BARBITURIC ACID DERIVATIVE)
WARNING: MAY BE HABIT FORMING
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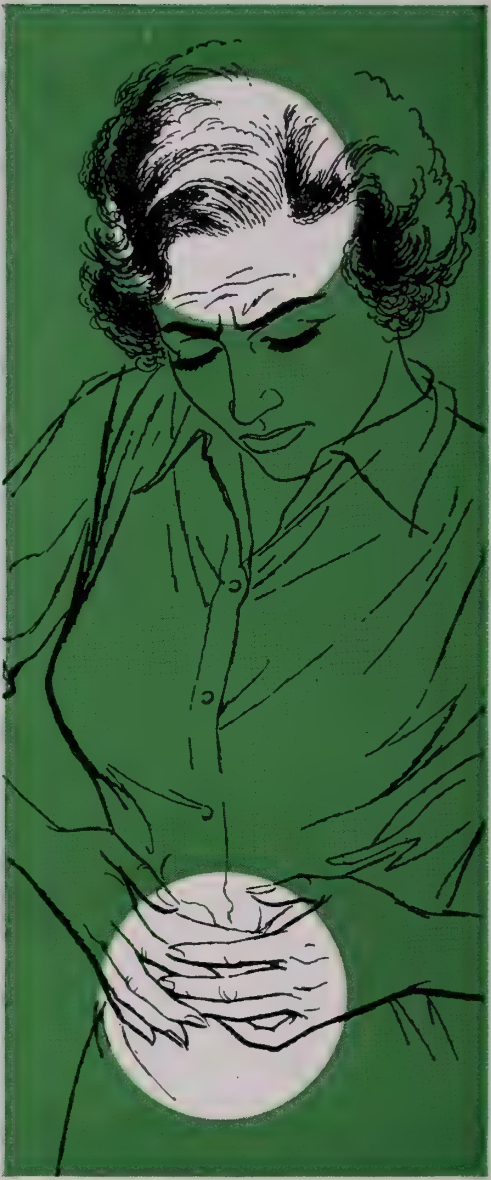
intermediate sedation and

relaxes 'G. I.' spasm.



Butadonna quiets the "brain-on-gut" influences by providing the smooth, intermediate sedative, butabarbital sodium, desirable in combination with the proven antispasmodic, belladonna extract. Butabarbital sodium is more rapidly eliminated than phenobarbital, and avoids the latter's cumulative effect.

Indications: Antispasmodic-sedative. Useful in the treatment of peptic ulcer, gastritis, duodenitis, irritable colon syndrome, ulcerative colitis, regional enteritis, and other conditions associated with gastrointestinal spasm. Also may be useful in functional dysmenorrhea.

Usual adult dosage is one tablet 3 or 4 times daily as needed.

Caution: Contraindicated in glaucoma and urinary retention. Reduce dosage or discontinue use in event of blurring of vision, dryness of mouth, tachycardia, or excessive drowsiness. Continued use of butabarbital sodium may be habit forming.

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The present study confirms the findings of Collis et al.,[1] and of Botha,[3] and has added other detail as to the relationship of the phrenic nerves to the margin of the hiatus in their course. Of more importance is their consideration and emphasis on the terminal course of the nerves to the crura when dealing with the surgical aspects of hiatus hernia repair and the control of gastric reflux. Accurate knowledge of the anatomical relationships facilitates surgical intervention and repair in the region and the retention of the normal physiological activities of adjacent structures encountered.

An analysis of these anatomical arrangements, which may be found bounding the esophageal hiatus,[2] leads to certain deductions as to the action of the muscle surrounding the hiatus on the esophagus and the cardiac notch. Although these deductions appear to be logical ones, there is a lack of experimental proof of the relative importance of the cardiac valve, cardiac notch and the hiatal musculature in physiological control of the opening into the stomach in the living state.

The details presented in the current study and in the others cited could be utilized to devise suitable experiments which would demonstrate the independent or concerted action of these parts in exercising control over this area. With such knowledge at hand, surgical procedures would be designed with greater assurance of success in alleviation of gastric reflux.

Warner S. Hammond, Ph.D.*
Syracuse, New York

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*Dept. of Anatomy, State University of New York, Upstate Medical Center.

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2. Collis, J. L., T. D. Kelly and A. M. Wiley: Anatomy of the Crura of the Diaphragm and the Surgery of Hiatus Hernia. Thorax 9:175, 1954.
3. Botha, G. S. M.: The Anatomy of the Phrenic Nerve Termination and the Motor Innervation of the Diaphragm. Thorax 12:50, 1957.

Violent Behavior Associated with Brain Tumor

> And earthly power doth then show likest God's
> When mercy seasons justice. — Shakespeare

DR. ARTHUR ECKER,* in presenting the clinical pathological conference, discusses in a very instructive way the interesting account of a patient with a brain tumor exhibiting behavioral aberrations. Such cases can represent baffling and challenging diagnostic problems. Dr. Ecker's precise and methodical analysis of the psychiatric and neurologic aspects of the case in arriving at the proper diagnosis is, therefore, worthy of careful review and study.

Controversy continues to be waged as to the causal relationship of behavioral changes occurring in patients with coexistent brain tumor. Public interest recently focused on this association following the mass killings in Austin, Texas. Charles Whitman, the slayer, had sought prior psychiatric help, and at autopsy was found to have a malignant brain tumor. Was the brain tumor responsible for his personality disorder? Or did the brain tumor only incidentally develop in a young man already afflicted with a preexistent character disorder? Judging by the widespread reporting and discussion surrounding this case it appears that society has a practical interest in the answers to those questions.

It is frequently pointed out in the medical literature that "psychiatric" patients are not more likely to develop brain tumors than those from the general population. But it is also important to stress that the incidence of brain tumor among patients in mental hospitals is three and one-half times that found among the general population.

That early behavioral changes associated with brain tumor are not unusual is shown in a paper by Strauss and Keschner.[1] They

Continued

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*See page 1885.

in chronic illness

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Vitamin B_6 (Pyridoxine HCl)	2 mg
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Vitamin C (Ascorbic Acid)	300 mg
Niacinamide	100 mg
Calcium Pantothenate	20 mg

Recommended intake: Adults, 1 capsule daily, for the treatment of vitamin deficiencies. Supplied in decorative "reminder" jars of 30 and 100; bottles of 500.

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found that mental symptoms were the earliest manifestations in 43% and changes in personality in 30% of frontal lobe tumors, and in tumors of the temporal lobe in 35% and 23% respectively. Behavioral aberrations associated with brain tumor take on a violent character in a high percentage of cases. Henry[2] observed that suicidal tendencies occurred in about 10%. The case discussed by Dr. Ecker was one in which violent behavior was associated with an acoustic neurinoma. Rubert and Remington[3] reported on 34 patients exhibiting psychoses due to brain tumor with violent behavior being recorded in 8 (assaultive behavior in 5 and suicidal attempts in 3) or 23.5%.

That there is a cause and effect relationship between intracranial tumors and associated behavioral changes is strongly suggested, not only by the higher incidence of such personality disturbances among brain tumor patients as opposed to the general population, but by the fact that such abnormal symptoms may disappear after successful removal of a coexisting brain tumor.[4,5]

It is, therefore, apparent that a substantial body of evidence exists supporting the belief that intracranial neoplasms can directly result in bizarre psychiatric manifestations which often take on an expression of violence. One would hardly draw this conclusion, however, from a review of the articles and commentaries which have appeared covering the story of Charles Whitman. Expressions published in the national popular news media[6,7,8,9,10,11] almost universally dissociated the deranged behavior he exhibited from the brain tumor which he harbored.

In strict justice, expert medical opinion must be objective in reporting to society. Society will rely on such information to develop preventive and other programs to cope with the social problems attending such crimes. Society will also rely on such information in passing judgment on the offender. In the case of Charles Whitman it would seem that medical evidence would support a more benevolent judgment than that which he has been accorded.

Harold D. Kletschka, M.D.
Syracuse, New York

References may be secured from the author or the reprints.

Test Your Word Score

Tomography — *a roentgenographic technique for showing a layer of tissues at any depth* (page 1829).
Hypocycloidal — *having a curve traced by a point on the circumference of a smaller circle rolling internally on the circumference of a larger circle* (page 1829).
Cassette — *a roentgenographic plate holder* (page 1832).
Proprioception — *awareness of stimulation within the tissues of the body* (page 1838).
Pannus — *a patch of membrane* (page 1841).
Halcyon — *tranquil, peaceful* (page 1847).
Amaurosis — *loss of vision* (page 1869).
Anosmic — *without a sense of smell* (page 1885).
Graphesthesia — *the sense which recognizes figures or numbers written on the skin* (page 1886).
Craniopharyngioma — *tumor of the hypophysis arising from neoplastic degeneration of squamous epithelial rests of Rathke's pouch* (page 1888).
Ayala index — *a quotient obtained by dividing the pressure after removal of 10 cc. of cerebrospinal fluid by that registered before such removal, and multiplying by 10* (page 1889).
Microgyria — *a malformation of the brain characterized by numerous small convolutions* (page 1890).

he kept using
the wrong code number

Payment to you is delayed unless we
know your code number. You don't want someone
else getting your check—do you!

BLUE SHIELD
OF MINNESOTA ®

You May Be Right

Each year, a statement of dues owed for membership in the Hennepin County, Minnesota State and American Medical Associations is mailed to the members. Frequently, as this year, the amount increased substantially.

Many doctors, faced with increasing society dues, coupled with a public image which has become steadily worse, wonder how much more political activity we are expected to pay for and, having paid for, suffer for.

I would like to hear reaction from other physicians. A poll to determine the position of a large group on dues, what is done with them, and to offer guidance, might be undertaken, if agreeable, by MINNESOTA MEDICINE.

The executive secretaries of the societies involved could be invited to set forth an account of their funds received and expended. If we can replace random criticism with a study of attitudes and an explanation of society activities, it will be a constructive step.

Angelo G. Johnson, M.D.
Bloomington, Minnesota

The Editor's Soliloquy

Convention Report

I suppose I should report on my visit to the Medical Meeting in San Francisco and incidentally mention my expense account. I took my wife along. How she can spot a chic and exclusive shopping center blocks and blocks away is amazing! She seems to have a sort of sixth sense in that direction. Like a thoroughbred she puts her nose up wind and proceeds briskly and confidently by the shortest route to Sak's Fifth Avenue, Bergdorf's, or Van Clief and Arpelt — in any city.

Well, she bought an elegant pair of 8½ quads brown with black toes, an equally elegant leather purse, and a pair of gloves to match. After that handsome purchase we boarded the squealing, screeching cable car for a ride to famous Fisherman's Wharf, where we invested 10 cents on a telescopic look at The Rock, and just barely got it focussed when it clicked off. Then we ambled casually over to take a look at Di Maggio's but found it much too expensive for a couple of Minnesotans on a sparse diet. So, after wandering about a bit longer absorbing the exotic aura of the Wharf: its unique aggregate of sights, sounds, and smells, we caught the cable car back to town. Returning to the Hilton, we bought a package of licorice and then went up to our room for our noonday siesta.

Total expenditure for one morning's ramble:	Cable car	,30
	Telescope	.10
	Licorice	.10
	Total	.50
Oh, I forgot shoes and purse and gloves ensemble:		134.50
	Tax	4.03
	New Total	139.03

Carl O. Rice, M.D.

Old Doc Hess says: Acne? That's just rowdiness in the blood from which one recovers as he gets older.

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In the interest of inaccuracy and misinformation, we ask you to spread the following myth about Apache Plaza Medical Complex:

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Other than pathology lab, radiology lab, professional pharmacy and ancillary services. That is to say, if you require facilities for major surgery, forget Apache Plaza Medical Complex. But if you can utilize the afore-mentioned allied services, together with offices designed to *your* specifications in the fastest growing area in the Twin Cities, give us a ring.

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But let's face it, Doctor, that's what makes a successful practice. If you're looking for more names in that appointment book, it's imperative that you consider Apache Plaza Medical Complex for your office location. It's in the heart of an already large residential area that is also the fastest growing area in the Twin Cities, with top incomes and young, growing families possessing superb credit. It's a natural if it's success you're after.

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Our Contributors

. . . . from

State University of New York
Upstate Medical Center

Julius B. Richmond, M.D.
Dean, The Medical Faculty

The future of any medical school rests with the direction and stimulus given to its development through its academic leadership. In 1965 Dr. Julius Richmond was appointed Dean of the Upstate Medical Center and under his able guidance the growth of the Center is anticipated with unbounded confidence.

In 1953 Dr. Richmond left his post as Professor of Pediatrics at the University of Illinois to assume the position of Professor and Chairman, Department of Pediatrics at the Upstate Medical Center. He continues to function in this capacity in addition to carrying on his many other important diverse duties and responsibilities.

As a clinician he has gained worldwide renown in the field of Pediatrics. He has expanded the dimensions of Pediatrics bearing on child problems

Continued

of all types. He has created a new model for the role of the pediatrician by emphasizing concern for the child as an entity with his own unique biological, environmental, and social problems.

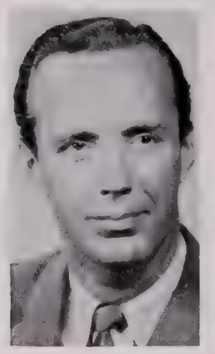
Outstanding scholarly and research contributions on his part span almost the entire spectrum of problems encountered in the field of Pediatrics and Child Welfare. Recognition has been accorded him for his conspicuous achievements by his being selected to hold many important offices in national medical societies. He exercises an important influence on the international medical scene as a member of the Expert Committee on Maternal and Child Health of the World Health Organization. For his distinguished contributions in the field of child development he was awarded the C. Anderson Aldrich Award in 1966.

Dr. Richmond brought great honor to the Upstate Medical Center in 1965 when he was appointed National Director of Project Head Start. Selection for this position is undoubtedly a reflection of his deep sense of social commitment. Mrs. Lyndon B. Johnson has identified herself with this program as one in which she has a special personal interest. On an occasion recognizing Dr. Richmond's contributions the First Lady saluted him saying, "Dr. Richmond is one of the most important commuters in Government." This remark gives insight into the importance of the program and suggests the taxing time commitments and activity of this demanding position.

Despite the enviable reputation he has achieved in his tripartite role as administrator, clinician, and civic leader, Dr. Richmond jealously guards his identity as a pediatrician.

Alfred S. Berne, M.D.

Dr. Alfred Berne was born in New York and received his M.D. degree from Duke in 1946. Following an internship in Chicago he took his residency training at Presbyterian Hospital in New York City. After serving on the faculty of the Department of Radiology at Columbia he came to Syracuse. He is currently Professor of Radiology at the Upstate Medical Center and is Chief of the Department of Radiology at Memorial Hospital, Syracuse.



David M. Connelly, M.D.

Dr. David Connelly graduated from the Temple University School of Medicine in 1954. He received his general surgical training at Memorial Hospital in Wilmington and with the U. S. Air Force. He continued his graduate training in Plastic and Reconstructive Surgery at Duke University and New York Hospital — Cornell Medical Center. Currently he is Instructor in Surgery (plastic) with the Division of Maxillofacial and Plastic Surgery at the Upstate Medical Center.

Dr. Arthur Ecker was born in New York City and graduated from Johns Hospkins Medical School in 1934. He was a Fellow in Neurology and Neurosurgery at the Mayo Clinic from 1935-39, during which time he was awarded the M.S. and Ph.D. degrees in Neurology from the University of Minnesota. He served as Clinical Professor of Surgery (Neurosurgery) at the Upstate Medical Center from 1955-63 and is now engaged in the practice of neurosurgery in Syracuse.

Arthur D. Ecker, M.D.

Dr. Daniel Elstein was born in New York City and received his M.D. degree from the Downstate Medical Center in 1958. He completed his internship and general surgery training at Montefiore Hospital. He then took his orthopedic surgery postgraduate work at the Memphis Veterans Hospital and Upstate Medical Center. Currently he is Clinical Instructor in Orthopedic Surgery at the Upstate Medical Center and Assistant Chief of Orthopedic Surgery at the Veterans Hospital in Syracuse.

Daniel Elstein, M.D.

Dr. Robert Gregg was born in New York and graduated from Syracuse University Medical School in 1934. Following his internship in Syracuse he took a Fellowship at the Mayo Clinic and received an M.S. degree in Surgery from the University of Minnesota in 1939. During his time spent at the Mayo Clinic he served as Assistant to Dr. Claude F. Dixon from 1939-40. From 1953-56 he was Chairman of the Department of Surgery at the Upstate Medical Center where he continues to serve as Professor of Surgery. He has gained distinction in the field of arterial surgery.

Robert O. Gregg, M.D.

Dr. Warner Hammond was born in Washington, D. C., and took his postgraduate training at Cornell, where he received his Ph.D. in Anatomy in 1937. He has been on the faculty of the Medical School in Syracuse since that time. At present he is Associate Professor of Anatomy at the Upstate Medical Center.

Warner S. Hammond, Ph.D.

Continued

E. Robert Heitzman, M.D.

Dr. E. Robert Heitzman was born in Syracuse and graduated from the New York State College of Medicine at Syracuse in 1951. He received his graduate training as a Fellow in Radiology at the University of Minnesota Hospitals from 1952-55. At the present time he is Associate Professor in the Department of Radiology and Director of the Division of Diagnostic Radiology at the Upstate Medical Center.

Harold D. Kletschka, M.D.

Dr. Harold Kletschka was born in Minneapolis and graduated from the University of Minnesota Medical School in 1947. He received his general and thoracic surgical training at the University of Michigan and the Downstate Medical Center. At the present time he is the U. S. Air Force Medical Service Liaison Officer and Assistant Professor of Surgery at the Upstate Medical Center. In addition, he is Chief of the Section of Thoracic Surgery at the Veterans Hospital in Syracuse.

Gordon K. Moe, M.D., Ph.D.

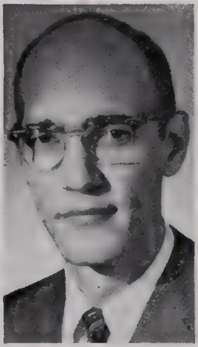
Dr. Gordon K. Moe attended the University of Minnesota Medical and Graduate Schools from 1934 to 1940, during which time he received the B.S., M.S., and Ph.D. (Physiology) degrees. He obtained his M.D. degree from Harvard in 1943. After leaving the University of Minnesota he became associated successively with Western Reserve, Harvard, Michigan, and the upstate Medical Center in Syracuse. He was the Chairman of the Department of Physiology at the Upstate Medical Center from 1950 to 1960, at which time he became Director of Research at the Masonic Medical Research Laboratory. He continues to serve as Research Professor of Physiology at the Upstate Medical Center. In 1958 he received an Outstanding Achievement Award from the University of Minnesota.

David G. Murray, M.D.

Dr. David Murray was born in Iowa and was granted the M.D. degree from Washington University in 1955. Following an internship at Vancouver General Hospital he took surgical training at the Upstate Medical Center and completed his postgraduate work in Orthopedic Surgery at the State University of Iowa. He is presently Associate Professor of Orthopedic Surgery and Chairman of the Department of Orthopedic Surgery at the Upstate Medical Center.

Irwin H. Pizer, M.S.

Mr. Irwin Pizer was born in Willington, New Zealand. He obtained an M.S. degree from Columbia University in 1960. His positions in the Upstate Medical Center are those of Associate Professor of Medical History and Director of the Library.



David B. Robinson, M.D.

Dr. David Robinson was born in Pennsylvania and received his M.D. degree from the University of Pennsylvania. Following an internship and medical residency at Geisinger Memorial Hospital he continued his graduate training at the Mayo Clinic from 1951-56, receiving his M.S. degree (Psychiatry) in 1957. He came to Syracuse in 1958, and since January, 1964, he has been Associate Professor and Acting Chairman of the Department of Psychiatry at the Upstate Medical Center.

J. Albert Schaefer, M.D.

Dr. J. Albert Schaefer was born in New York and graduated from the Long Island College of Medicine in 1948. He took his graduate training at Western Reserve and the Crile Veterans Administration Hospital. At present he is Associate Professor of Pathology at the Upstate Medical Center and Chief of Laboratory Services at the Veterans Hospital in Syracuse.

David B. Stark, M.D.

Dr. David Stark was born in Canada and received his medical degree from Toronto in 1943. He obtained his graduate training as a Fellow in General Surgery and Oral and Plastic Surgery at the Mayo Clinic from 1946-51. He received an M.Sc. degree in surgery from the University of Minnesota in 1948. He is now Clinical Professor of Surgery (plastic) and Chairman of the Division of Maxillofacial and Plastic Surgery at the Upstate Medical Center.

Continued

Martin Wynyard, M.D.

Dr. Martin Wynyard was born in Germany, received his medical degree from London University in 1949, and obtained his Fellowship from the Royal College of Surgeons (England) in 1953. He obtained his general and thoracic surgical training at some of the world's leading medical centers in Great Britain and continued his training in this country at Lahey Clinic and the Upstate Medical Center. At the present time he is carrying out cardiovascular surgical research at the Veterans Hospital in Syracuse and is engaged in the practice of thoracic and cardiovascular surgery.

Parinaud's Oculoglandular Syndrome

Synonyms: *Parinaud's conjunctivoadenitis syndrome; cat-scratch-oculoglandular syndrome.*

Conjunctivitis, retrotarsal conjunctival granulations, regional preauricular and cervical lymphadenitis, and fever characterize this syndrome. It was first described by Parinaud (1889); Gifford suggested the eponymic designation (1898).

Clinically the condition may be recognized by the appearance of a granular and sometimes ulcerative conjunctivitis and early swelling of the anterior cervical and parotid glands. Other local tissues, such as the cornea, are not involved. A moderate febrile reaction accompanies the infection. It is almost invariably unilateral. The etiology has long been puzzling. Transmission from patient to patient does not seem to occur. Among the suspected causative agents are tularemia, leptothrix, sporotrichosis, lymphogranuloma venereum, and a yeastlike organism. An intradermal test with an antigen of cat-scratch fever frequently gives a positive reaction. Increasingly, Parinaud's oculoglandular syndrome and cat-scratch syndrome are regarded as having a common etiology, the conjunctivae being considered the site of primary infection. Spontaneous recovery occurs but may require a few weeks or a few months.

Durham, Robert H. — Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

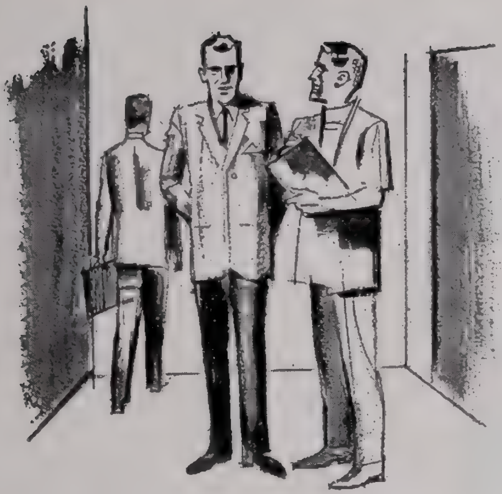
As for style of writing, if one has anything to say; it drops from him simply and directly, as a stone falls to the ground. . . . A sentence should read as if its author, had he held a plough instead of a pen, could have drawn a furrow deep and straight to the end.

Thoreau Letters

Three things cannot be taught — generosity, poetry and a singing voice.

— Irish proverb

When a thing is funny, search it for a hidden truth. — George Bernard Shaw



Curbstone Consultation

Respiratory Tract

Question: What is the relative incidence of cancer of the respiratory tract in the male compared to the female?

Answer: It occurs about four or five times more frequently in the male, accounting for 18-20% of all cancer in that sex.

Harold D. Kletschka, M.D.
Syracuse, New York

Bronchogenic Carcinoma

Question: I have a patient with bronchogenic carcinoma and myasthenic-like syndrome. Does the existence of this latter manifestation mean that the patient's tumor is incurable?

Answer: About 15% of patients with bronchogenic carcinoma will exhibit neuromyopathic findings. The myopathic-myasthenic syndromes are the most common. It is felt that the myasthenic-like symptoms result from a defect in neuromuscular conduction and a polymyositis with primary degenerative changes in the muscles. The syndrome is characterized by weakness of the proximal muscles of the extremities, particularly the thighs, but does not in itself signify that the tumor should be considered incurable. As a matter of fact the symptoms may disappear following removal of the primary lung tumor. It is important to differentiate the symptoms encountered in such neuromyopathies from those of metastatic disease. Patients with this syndrome may experience a marked sensitivity to curare and depolarizing relaxants.

Harold D. Kletschka, M.D.
Syracuse, New York

Weightlessness of Manned Space Flight

Question: Has the weightlessness of manned space flight resulted in untoward cardiovascular changes?

Answer: Cardiovascular function is altered during manned space flight. However, it is difficult to assign such changes to a single environmental factor such as weightlessness. The changes observed are similar to those seen in cardiovascular deconditioning consisting of decreased exercise and orthostatic tolerance. Nevertheless, it appears that with currently available life support systems weightless flight can be tolerated for a period of at least one month.

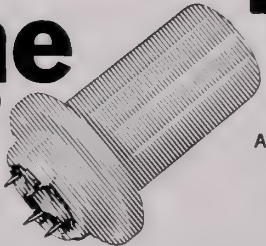
Harold D. Kletschka, M.D.
Syracuse, New York

what time is it?

For the past
two years
there's been
one new case
of active tuberculosis
reported for every
four thousand
of U.S. population.

it's time to tine.

Tuberculin,
Tine Test
(Rosenthal) Lederle



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The Viewing Box

A 39-YEAR-OLD female had been in the hospital, February 1965, with an acute exacerbation of rheumatoid arthritis. At that time the chest roentgenogram was negative. She had had rheumatoid arthritis for thirteen years. She had been treated with various steroid derivatives continuously over this period.

In late November she was admitted with episcleritis and the usual painful joint complaints but no chest complaints. An admission chest roentgenogram (Figures 1 and 2) disclosed a left pleural effusion with partial atelectasis of the left lower lobe and lingula of the left upper lobe. It was also felt that a partial left pneumothorax or multiple bleb formation was present. Cardiac fluoroscopy and an esophagram showed cardiac enlargement and elevation of the apex of the heart. Planigrams disclosed a mass density in the left lower lobe area. Bronchoscopy with followup bronchography (Figures 3 and 4) demonstrated elevation of the lingula of the left upper lobe and deviation and compression of the bronchi of the left lower lobe posteriorly. The mass causing this deviation appeared to contain a loculated air or bleb formation. Thoracentesis yielded only 2 cc. of fluid. Laboratory findings were within normal limits. The thoracentesis fluid culture revealed no growth.

What Is Your Diagnosis? (See next page.)

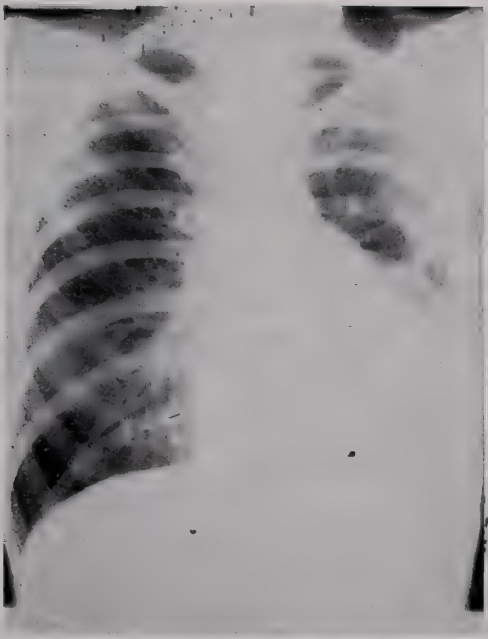

Figure 1

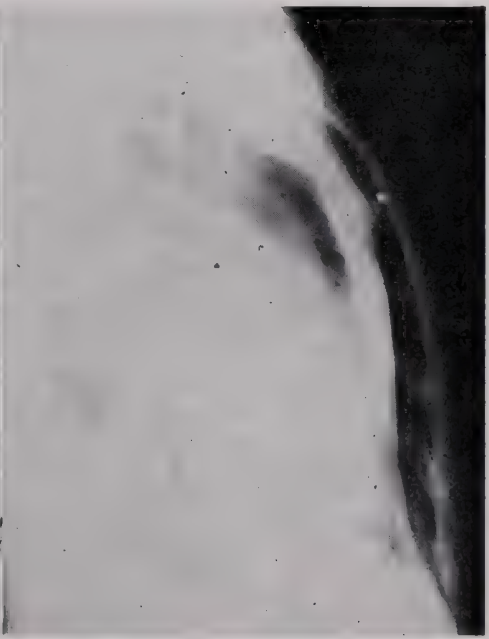

Figure 2

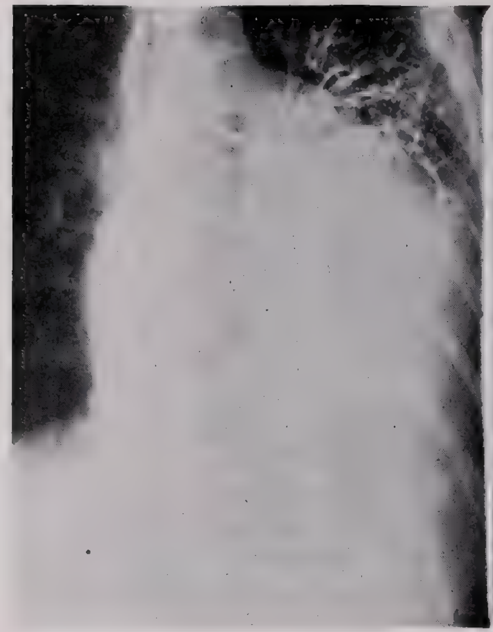

Figure 3

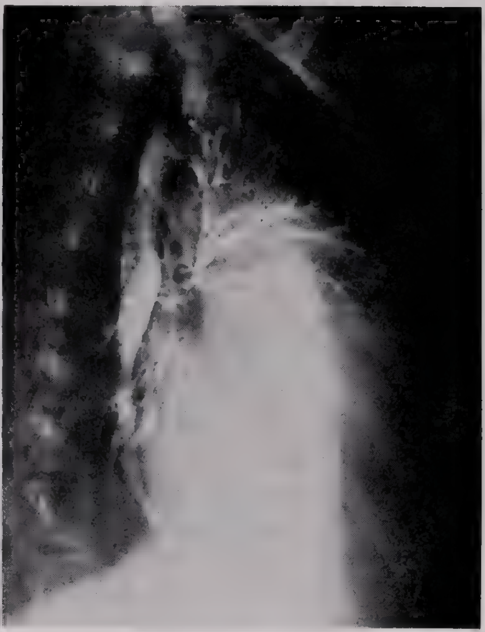

Figure 4

Diagnosis: Empyema.

The patient declined to have any further procedures and went home. One week later she was found dead in bed.

An autopsy was performed. The left pleural cavity contained a greenish-yellow thick loculated empyema of 500 cc. plus. The pleura was very thick and irregular with multiple adhesions and pockets including adhesions to the pericardium. The right lung weighed 325 grams and was unremarkable but the left lung weighed only 125 grams and was markedly compressed. The pericardium was thickened and pericarditis with thick fluid was present. Multiple small abscesses were found in the brain, heart, spleen and lymph nodes. The adrenal glands were atrophied. Special stains of these abscessed areas revealed no organisms. Cultures over a prolonged period of time revealed no growth.

The modern medical literature of today has scant reference to empyema. Not too many years ago empyema was a common diagnosis. In the present case a pneumonia, pleurisy, empyema and, finally, pyemia did occur but without the usual clinical manifestations. This does happen in the chronically debilitated patient, particularly when the prolonged use of steroid and antibiotic therapy has been necessary. Remember—empyema still does occur.

Milton R. Gilchrist, M.D.
Midway Hospital
St. Paul, Minnesota

Truth

On the mountains of truth you can never climb in vain: either you will reach a point higher up today, or you will be training your powers so that you will be able to climb higher tomorrow. — Nietzsche

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A man is really a success when flattery gives him a headache instead of a big head.
— Ralph Bellamy

Neurological Conference

Progressive Spastic Quadriplegia[*]

Doctor Ross Olson[**]

The patient is a 58-year-old former engineer who came to the University Hospitals for the first time in May, 1966. His chief complaints were a 10-day history of hemoptysis and an 11-year progressive spasticity of his extremities. The hemoptysis appeared acutely and was accompanied by right chest pain. He said that he had coughed up dark clots, followed by bright blood which had not appeared to be mixed with mucus. After continuing for some time, this seemed to subside. He had also noted that his stools were darker then. His family physician examined him at that time and took a chest x-ray which was negative; however, on laryngoscopy he found what he considered to be a tumor of the vocal cords.

Past History and Findings

The history of the spasticity began in 1955 when the patient first noticed that his left foot shook on the clutch as he was driving. Thereafter he had a gradual increasing difficulty in walking, and in the spring of 1956 he was referred to a neurologist.

Tenderness was found at the level of the T 10 vertebra and an erosion of that bone was present on the x-ray. An exploratory operation revealed a general constriction of the thoracic cord, which appeared to be a degenerative lesion rather than a tumor. One year later an electroencephalogram, cervical myelogram, and cervical tomograms were negative. Pneumoencephalography suggested a diffuse narrowing of the cervical cord but no evidence of tumor.

By 1958 he was using a cane, and within a short time he needed two. In 1958 his left eye suddenly became amaurotic.[†] Neurological consultation was obtained again at that time and it was thought the most likely cause was an embolic phenomenon. He has had no recovery of his vision

Continued

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[*] Sponsored by the U. S. Public Health Service Grant N2502A63. These conferences are an integral part of the Comprehensive Clinic Program at the University of Minnesota Hospitals. The pediatrics conferences are held every Wednesday from 1:00 to 3:00 p.m. The adult conferences are held every Thursday at 4 p.m. Co-ordinators for the project are Dr. Charles Branthaver and Dr. Edward Defoe in Pediatrics, and Dr. Robert Soll, in Adult Neurology.

Held on May 12, 1966.

[**] Student doctor, University of Minnesota.

[†] See Test Your Word Score Page 1855.

Continued

in that eye. In 1959 he spent two months in a private hospital in Denver, Colorado, where he obtained some subjective relief. They prescribed honey and fruit juice, which he still takes. Soon he was confined to a wheelchair and his company transferred him to a desk job. Involvement of his hands became more evident in 1960, and within one year he had to quit work entirely. Difficulty talking appeared in 1962 and trouble swallowing followed within the next two years.

In the past he has had no serious illness except what he called pleurisy in 1951. As a four-year-old child he had a back injury which was followed by opisthotonus for 24 hours, after which he apparently recovered completely. The presumptive diagnosis at that time was subarachnoid hemorrhage. He has smoked for 40 years, using as many as four packs a day at times. He currently smokes about one half to one pack a day, but in the very early part of his illness he was smoking up to four packs a day, since his gradual incapacitation in his work gave him more time for smoking. He was accustomed to an executive type position.

Physical Findings

On physical examination he appeared to be quite thin with a very tense face and looked quite old for 58 years. When he spoke he had an extremely severe dysarthria which made his speech virtually incoherent. His wife apparently could understand him and she would translate. His mental status was entirely intact. A left carotid bruit was noted and coarse rales were present in his lungs bilaterally. His blood pressure was 240/105 mm. Hg. and a grade ii/vi systolic ejection murmur could be heard at the apex of the heart. Moderate dependent ankle edema was present. Subjectively, no vision was present in the left eye, even to a flash light, and acuity in the right eye was slightly decreased. Funduscopic examination showed optic atrophy in the left eye and findings consistent with grade 2 to 3 hypertension in both fundi. He had generally hyperactive reflexes with positive toe signs, sustained clonus in the ankles which at times was spontaneous, a hyperactive jaw jerk, and positive palmomental reflexes. A generalized weakness of all muscles was present, especially in the hamstrings and adductors of the thighs. No obvious muscle atrophy was apparent.

Laboratory Data

Laboratory investigation showed a normal hemoglobin and white blood cell count. The erythrocyte sedimentation rate was 43 mm./hr. Urinalysis and a Schilling test were both negative. The cerebrospinal fluid showed a protein of 63 mg. %. Sputum culture revealed many gram-positive cocci in pairs, chains and clusters; there were also many diphtheroids and a few gram-negative rods. Electromyography showed evidence of denervation in the hamstrings and gastrocnemii. The chest x-ray revealed old apical pleural changes present bilaterally. Planograms of the right upper lobe of the chest showed pleural thickening of the right apex with some fibrotic strands extending into the parenchyma. There was also some calcification within this region. An upper gastrointestinal series, esophagram, and skull x-rays were normal. Cervical spine x-rays showed mild, degenerative changes. The disc spaces were fairly well preserved except for the C5 space, which showed some mild narrowing. At the C5 level there were some posterior spurs present. The Mantoux test was positive.

The Evaluation

Discussion with patient's wife.

Dr. Robert Soll* (to the patient's wife)

Do you have any special problems such as getting him in and out of bed or taking him to the bathroom?

Patient's wife

I let him do those things by himself. I got some strong luggage handles and fastened them to the head of the bed so he could hold on to them to roll over. He has a double bed because he would roll over and off the single bed that he had. Just recently we had to get a new toilet. He could put his hand on the tank of the old toilet which was fastened to the wall and then have braces up on the wall in order to transfer; however, I have just gotten those guards for the new toilet. They fit right over the side of it; so it was getting harder for him to turn from the wheelchair to the toilet.

Dr. Soll

Is there any problem with bathing?

Patient's wife

Our house is real old. He could get right up under the washbowl in the wheelchair; this wouldn't have been possible with a foot rest on his chair. He never wanted one because then he couldn't get up to things. He could wash himself in front; so I washed his back while he was sitting at the washbowl. He did his feet separately.

Dr. Soll

Has he ever choked or had trouble swallowing?

Patient's wife

He feeds himself and he does choke easily. I was afraid that this might happen when I was at work.

Dr. Soll

Do you know anything about the injury he had when he was four years old?

Patient's wife

All I know is that they lived on a farm in South Dakota. First of all he rolled off this load of cobs. I thought his mother had said that he hit a part of the wagon, but now he says that he hit the ground. He was semiparalyzed for 24 hours or so, and he couldn't lie down flat because he was bowed up according to his mother. I think his head and buttocks touched the bed but his shoulders didn't. The doctor thought it was spinal meningitis; so he had to send to Sioux City, Iowa, for serum, but when he came back the next day his patient was better. His mother said she alternated hot packs and cold packs on him all night long.

Dr. Frank Meelhuysen**

How much help does he need in dressing?

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*Neurologist, University of Minnesota Hospitals.

**Assistant professor, Physical Medicine and Rehabilitation, University of Minnesota Hospitals.

Continued

Patient's wife

He does all his dressing, except that certain shirts give him a little difficulty.

Medical Evaluation

Dr. John Bergstrom*

This gentleman's presenting complaint and the reason he sought a doctor after being totally incapacitated for many years by a spastic disease was "spitting up blood," which apparently was not mixed with sputum. Significantly in the past he has been a heavy smoker, and, in addition, he has suffered from probable aspirations during the past two years. He has had decreasing amounts of sputum production in recent years; at one time he was bringing up quite a bit of orange-tinged sputum which has diminished with his decreased ability to cough.

A partially compensated paralysis of the left vocal cord was found. This means that the left vocal cord was immobile in the paramedian position; no evidence of a neoplastic process of the cords was found and the remainder of the ear, nose and throat examination was within normal limits. The chest x-rays taken at admission initially were read as negative for his age; however, on review of his films there was evidence of some fibrotic-appearing material in the right upper lobe. This was somewhat more apparent in the lordotic view of the apex. A similar finding had been reported in 1956. Our skin tests show a positive response for intermediate strength purified protein derivative (tuberculin).

There was a considerable degree of lability in his blood pressure ranging from about 180 to 220 mm. Hg. systolic and from 90 to 140 mm. Hg. diastolic. An intravenous pyelogram was obtained to rule out the possibility of renal disease. Although it was not a perfectly adequate study due to poor visualization of the nephrogram on the left, the excretion appeared to be equal and essentially normal. Examination of the urinary sediment was negative and the blood urea nitrogen was 11 mg. %.

Neurological Evaluation

Dr. Soll

It is interesting that this patient's past history includes a severe back injury. According to the history, he apparently developed opisthotonus, which would indicate a diffuse meningeal irritation. The general clinical picture and course of the disease on the other hand is suggestive of a pseudobulbar palsy and spastic quadriplegia. In this condition the involvement would be present in the corticospinal tract above the level of the medulla. The usual etiology is cerebral vascular disease but other degenerative conditions may also cause it.

In addition to difficulty walking, these patients demonstrate severe dysarthria and dysphagia, but our patient does not present altered emotional reactions such as are often seen in this condition. Eventually these patients develop difficulty from upper respiratory infections or may choke; however, they may survive many years if these complications are guarded against. The only evidence of lower motor neuron involvement below the level of the brain stem is the denervation potentials shown on the electromyogram of the lower extremity musculature.

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*Medical fellow, University of Minnesota Hospitals.

Physical Medicine Evaluation

Dr. Meelhuysen

The patient is able to do his transfer activities independently at home, such as from bed to wheelchair and back, and from wheelchair to toilet. Of course, with the amount of spasticity he has, it requires considerable effort to make the transfer. Discrepancy between the height of the bed and his chair makes the transfer much more difficult for him. In addition, he can hardly stand because of the contractures in hips and knees, plus thigh adduction spasticity which causes crossing over of the legs. There is marked clonus in his ankles. Another feature apparent in this patient is his tight hamstrings, most likely due to spasticity and positioning of the legs. This contributes to his knee flexion contractures.

As far as joint range of motion in the upper extremities is concerned this is still in functional range. One usually sits with the arms internally rotated at the shoulders with pronated forearms and flexed elbows, a posture which becomes more evident when spasticity is present. In this patient there is already some limitation of external rotation in his shoulders and only 5-10 degrees of supination in his arms. In general his shoulder range is essentially normal for his age although he lacks about 30° flexion and abduction on both sides. There is clonus in the shoulder internal rotators, and the pectorals are spastic also. The latter can become so tight that the arm is continually kept in adduction. Both flexion and extension of the elbow demonstrate increased stretch reflex.

Another feature in this patient is the function of his tongue and its relationship to his dysarthria and dysphagia. He demonstrates marked weakness on tongue protrusion. Retraction and elevation of the tongue are important for moving a food bolus backwards. The former can be tested by retracting the tongue against manual resistance. The tip of the tongue is thereby held between the examiner's thumb and digits ii and iii while he exerts a pulling force. This maneuver occasionally can cause regurgitation. His gag reflex is reduced. His coughing force is very poor because of poor glottis control. He only clears his throat when he makes an attempt to cough. His voice is hoarse. These signs make one suspicious of bulbar involvement.

Psychological Evaluation

Dr. John Brantner*

The patient has an interesting psychological report. As far as could be determined from the Peabody Picture Vocabulary test, the patient has an intact personality and a relatively intact intelligence. His personality is pleasing and attractive. In the psychological testing situation he is persistent and patient and does not display temper or frustration. He is socially perceptive and responsive and less worried about his own feelings than he is concerned with the feelings of others. He displays a general thoughtfulness, politeness, and sweetness of temperament that continues in what must be very difficult situations. His vocabulary of understanding is large and does not appear to be impaired. He is in the top 10% of the general population in the number of words whose meaning he understands. The patient was given the Leiter International Performance Scale test.** His performance on a wide range test is lower; about 80% of the

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*Associate professor, Clinical Psychology, University of Minnesota Hospitals.

**Designed for people who have marked physical disability.

Continued

general population of non-handicapped adults do better than he does. His performance is uneven (as might be expected). The Leiter International Performance Scale test calls for very fine visual discriminations; he had to use his spectacles and a hand magnifying glass to see these. He found the manipulation of small blocks difficult, but he persisted to solution in many cases. His number sense is very good, and he is superior in his manipulation of numerical concepts. Some other abstract intellectual operations proved difficult; he had trouble with classifications and with mosaic block designs. He appeared to "get the idea" in these cases but was unable to execute them. Fatigue may have operated here also. He was persistent and cooperative, but the testing took four to five hours.

Social Service Evaluation

Miss Annie Laurie Baker*

The patient was born in South Dakota. His father was a farmer. When he was about seven his parents were divorced and his mother remarried. The patient did not get along with his stepfather and went to be with his father in Nebraska when he was twelve years old. He stayed with him through his sophomore year in high school and then got a job working on a ranch taking care of horses.

When he was eighteen, he hitch-hiked and walked to Idaho to get a job in a lumber camp. This was during the depression. In 1930 he joined the marines and was stationed in the Orient, spending most of his tour of duty in Shanghai. He was discharged in November, 1935.

While he was visiting his brother who was a farmer in Nebraska, his brother had an accident and the patient remained to take care of the cattle. In the spring of 1936 he went to Fairmount, Minnesota, where his father had a job as a night watchman at the canning company, and obtained employment there in the refrigeration department. As he showed considerable promise, the company paid for correspondence courses in refrigeration engineering. Incidentally, he had completed high school by correspondence also.

When the company sold out to the Birds Eye company, he was transferred to the plant in Waseca. Subsequently, when he became confined to a wheelchair, he was transferred to the purchasing department. He has not been able to work for the past five years. He belongs to the Masonic Lodge, was active in church affairs, enjoyed sports and had many friends. His wife works as an office clerk from 5 P.M. to 1:30 A.M.

The family own their own home, a modern one-story six-room bungalow. Their income consists of the patient's total disability payments and his wife's earnings. The County Welfare Department has given State and University papers to pay that portion of the medical expenses not covered by insurance.

This is a family of competent resourceful people — able to handle adversity. The patient has been without a salary for several years; but together he and his wife have been able to raise and educate their three children, own their home, and continue free from debt.

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*Director, Social Service Department, University of Minnesota Hospitals.

The Management

Management of the Hemoptysis

Dr. Bergstrom

We still are left with the primary medical problem of not knowing the source of his hemoptysis. Does he have tuberculosis which is now activated? We do not really see any evidence for this, but we are planning to do planography in hopes of getting a little better picture of his apices. This man may possibly have chronic bronchitis without any finding on chest x-ray. In some of the recent literature the incidence of small amounts of hemoptysis with such a condition is quite high, but these patients almost always have a great deal of sputum production. Whether or not this man's sputum production is absent because of his neurological disease, we are seriously considering that he should have bronchoscopy because of the unilateral vocal cord disease, the episode of hemoptysis, and the history of heavy smoking. There is a remote possibility of an occult carcinoma of the lung which could be seen at the level of the carina.

Dr. Soll

Could this be done safely?

Dr. Bergstrom

Yes.

Dr. Richard Magraw*

What is his respiratory reserve?

Dr. Bergstrom

The vital capacity is 1.2/2.0. He virtually cannot count at all past four or five. I have seen patients with vital capacities less than one tolerate bronchoscopy very well. Bronchography is a different situation; it would be a relatively dangerous procedure.

Dr. Soll

Is there any evidence that the bleeding originated inside of the mouth? Doesn't he have very bad teeth?

Dr. Bergstrom

He has a very bad dental condition, but there is no evidence of gingival bleeding. The dentists are scheduled to see him.

Management of the Neurological Condition

Dr. Soll

There is no specific therapy known that will retard the progressive neurological involvement in this condition. Good nursing care, however, is extremely important in making the patient as comfortable as possible.

The carotid bruit which this patient has is undoubtedly significant but I am hesitant to recommend investigation by angiography now in view of his hypertension and the far advanced stage of his neurological condition.

Dr. Meelhuysen

In order to prevent limitation of shoulder movements, one can teach the patient not only to lie with his arms along his sides, but also to put his hands behind his neck while supine. This maneuver abducts and externally

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Continued

rotates the arm, enabling it to maintain its range in these directions. It is also good to know which muscles of the forearm are spastic, because of their tendency for structural shortening. His wrist flexors are tight. Keeping the wrist and metacarpal phalangeal joints flexed, a non-sustained clonus in the long finger flexors can be demonstrated by subjecting each finger individually to a sudden extension stretch.

Presently we are able to reduce spasticity in isolated and selected muscles by motor point blocking.* Partial blocking of the major shoulder adductors make abduction easier and could relieve discomfort on motion in this joint. It is my impression that spastic and tight shoulder adductors can pull the head of the humerus downwards, making it pivot in the wrong position in the glenoid fossa in the early phase of abduction. I have seen several cases in which the capsule has been unduly stretched, causing shoulder pain on motion; in these cases blocking the pectoral major and/or the teres major and latissimus dorsi muscles have alleviated the discomfort a great deal. Our patient does quite well on shoulder movements although he may have to limber up a bit. I would not suggest any motor point blocking of his long finger flexors at this time for the simple reason that his finger dexterity is still functional. Finger extension exercises should be done, nevertheless. If one decides to block the long finger flexors at a later date, blocking the flexor digitorum sublimis muscle, which inserts at the base of the middle phalanx of each finger, is preferable. I have noticed particularly in these patients that a spastic flexor digitorum profundus muscle enables them to use their fingers as a hook; however, if this deep long finger flexor muscle is blocked, the hand cannot be used even as a hook.

For the lower extremities I would suggest blocking of selected muscles followed by prolonged stretching of the contractures. This would help him in his transfer activities. In order to relieve the marked ankle clonus, it is important to determine whether the clonus is in the gastrocnemius, in the soleus or in both. His clonus is primarily located in the soleus; so there is no reason to block the gastrocnemius. When checking for ankle clonus, I do it in two ways: First, I extend the knee as much as possible and then try to elicit clonus by dorsiflexing the foot. In this position very little clonus is produced in this patient; however, if I then bend his knee, the clonus becomes more intense. In the latter position, the gastrocnemius becomes more relaxed and the soleus comes under more tension. This indicates to me that the clonus is primarily located in the soleus. With this finding, blocking of the soleus only should eliminate his ankle clonus. His standing posture will also improve, because the plantar flexion spasticity forces him to bear most of his weight on his forefoot, making him more unsteady on stance. Since the patient sits most of the day time, he should be instructed to lie prone to counteract the tendencies for developing flexion contractures in the hips as well as in the knees. One of our recommendations at the time of his discharge will be to alternate sitting and prone positions more adequately, if further deterioration of flexion contractures is to be avoided.

The degree of contractures he has at the present can be alleviated by reduction of his spasticity followed by prolonged stretch. The former permits stretching measures to be more effective. The reason for this is that any transfer activity becomes easier and consequently requires less energy when fewer contractures are present. Thus improving his standing posture is a goal within his reach.

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*Motor point blocking — temporary interruption of motor innervation by injection of dilute phenol solution into muscle near point at which motor nerve enters muscle.

The gag reflex can be used as a functional exercise for the entire oropharynx; this should be done preferably before meals. The patient mentioned that he has no wheelchair with removable arm rests of the desk type. For a person in his situation transfer activities would be easier with this added feature. He could also move closer to the table. Another desirable accessory for his wheelchair are leg rests that allow leg elevation. Although his desire is to be able to walk again, I will not set this as an immediate goal, since he has not walked for at least six years.

Conclusions

1. Complete bronchoscopy in order to determine, if possible, the cause of the hemoptysis.
2. Insure good nursing care in the home to prevent further contractures and minimize the possibility of aspiration.
3. Undergo a progressive program of therapy as outlined above to make the patient more independent and possibly improve his standing posture.
4. Obtain a new wheelchair for the patient.

Addendum

A bronchoscopic examination was performed which revealed no satisfactory explanation for the patient's hemoptysis. After the recommended procedures were done to reduce the spasticity and contractures of the lower extremities, progressive training was begun to facilitate transfer activities and ambulation. By the time of discharge from the hospital, the patient was ambulating short distances with two broad-based canes.

Robert Soll, M.D.
University of Minnesota Hospitals

Participating in the conference were: Student Doctor Ross Olson; Dr. Robert Soll, Neurologist; Dr. John Bergstrom, Medical Fellow; Dr. Frank Meelhuysen, Assistant Professor, Physical Medicine and Rehabilitation; Dr. Richard Magraw, Director, Comprehensive Clinic Program; Miss Annie Laurie Baker, Director, Social Service Department and Dr. John Brantner, Associate Professor, Clinical Psychology.

Buckle Up

Never stop on a freeway except for an emergency

If you need to stop on a freeway, signal as early as possible. Drive promptly onto the shoulder of the road. If you need help tie a handkerchief to the radio antenna, raise the hood, or tie a handkerchief to the left door handle. At night use flares or reflector or leave the car lights on. Leave the car only from the right side, and do not stand on or close to the roadway. Don't hitchhike. Stay with your car until help arrives. Freeways are patrolled regularly.

Don't stop if you observe a disabled auto on the freeway. Instead, report it to the authorities at your first opportunity.

Better to sink beneath the shock
Than moulder piecemeal on the rock. — Byron

MOLECULAR REMODELING—

laboratory exercise or clinical necessity?

More than twenty-five years have passed since the discovery of the diuretic activity of sulfanilamide started pharmacologists on a succession of molecular remodelings to find the ideal diuretic.

Diuresis—a sought-after clinical effect from an unwanted side effect

It started in 1937 when a clinician reported that the administration of a sulfonamide was sometimes accompanied by an unexplainable side effect—metabolic acidosis.[1] Three years later the side effect was explained. The sulfonamide radical of sulfanilamide inhibited carbonic anhydrase,[2] the enzyme responsible for converting carbon dioxide and water to hydrogen ions and bicarbonate ions.

Later, other investigators showed by dog experiments that metabolic acidosis probably resulted when the inhibition of carbonic anhydrase upset the exchange of hydrogen and sodium ions, causing increased excretion of sodium as the bicarbonate.[3]

It was twelve long years after the first report of the unexplainable side effect (metabolic acidosis) that it was finally shown that large doses of sulfanilamide administered to edematous patients were indeed capable of promoting diuresis.[4] However, the possibility of toxic effects from its prolonged use and its relatively weak diuretic action made it impractical for clinical use as a diuretic.[5]

Because the inhibition of carbonic anhydrase seemed to be the key to effective diuresis, investigators began to look for more potent enzyme inhibitors —in the hopes that they would be more effective diuretics.

The most important of these early compounds, acetazolamide, enjoyed several years of fairly wide clinical use.

Its carbonic anhydrase inhibitory activity was several hundred times greater than that of sulfanilamide.[6] The increase in inhibitory activity, however, increased not only the excretion of sodium and bicarbonate ions, but also the excretion of potassium.[7] And, like its predecessor, acetazolamide precipitated mild acidosis. Its prolonged use could result in hypokalemic acidosis.[7]

The 'thiazides'—an answer to the metabolic acidosis caused by carbonic anhydrase inhibition

Despite the fact that the sulfonamide group appeared to be responsible for carbonic anhydrase inhibition which in turn appeared to be responsible for diuresis, investigators began to synthesize compounds with structural alterations to the sulfonamide group.

The first major breakthrough came with the synthesis of chlorothiazide. Altering the sulfonamide group did indeed alter the ability of chlorothiazide to inhibit carbonic anhydrase—it was only 1/10th as potent as acetazolamide in inhibiting the enzyme.[8] Despite the drop in inhibitory potency, however, chlorothiazide proved to be an effective diuretic—an observation that led to the conclusion that its diuretic action was due to some mechanism other than its action on carbonic anhydrase.[9, 10]

For effective diuresis, chlorothiazide was administered in daily dosages ranging from 250 to 2000 mg.[11] It increased the excretion of sodium and chloride; and, to a lesser extent, potassium and bicarbonate.[11] The excretion of potassium appeared to be maximal at higher dose levels at which, theoretically, the carbonic anhydrase inhibitory effect is more active.[11] Its prolonged use, therefore, could sometimes result in metabolic hypokalemic, hypochloremic alkalosis.[7]

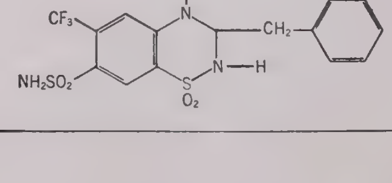
Naturetin—effective diuresis with more favorable electrolyte balance

Other thiazides followed—with improvements being aimed at two particular areas: 1. attempts to increase diuretic action in relation to the milligram potency of the drug, and 2. attempts at a more favorable sodium/potassium ratio in the urine, i.e., to decrease the excretion of potassium while maintaining the excretion of sodium.[12]

One of these, Naturetin, Squibb Bendroflumethiazide, has made advances on both these points. "By adding a 3-benzyl radical to hydroflumethiazide a rather dramatic reduction in dose range is accomplished. With this drug, effective sodium excretion is obtained with doses between 2.5 and 10 mg., which is a 200 to 1 ratio as compared to chlorothiazide..."[13]

Moreover, due probably to its virtual lack of carbonic anhydrase inhibition, Naturetin (bendroflumethiazide) has been shown to cause less potassium and bicarbonate loss and less alteration in urinary pH than either chlorothiazide or hydrochlorothiazide.

Naturetin is outstandingly effective not only in establishing, but also in maintaining, excretion of retained fluid in edematous patients. And its duration of action is sufficiently prolonged to allow a single daily administration in most patients. Naturetin is also an effective antihypertensive agent.



Contraindications: Severe renal impairment; previous hypersensitivity.

Warning: Ulcerative small bowel lesions have occurred with potassium-containing thiazide preparations or with enteric-coated potassium salts supplementally. Stop medication if abdominal pain, distension, nausea, vomiting, or G.I. bleeding occur.

Precautions: The dosage of ganglionic blocking agents, veratrum, or hydralazine when used concomitantly must be reduced by at least 50% to avoid orthostatic hypotension. Electrolyte disturbances are possible in cirrhotic or digitalized patients.

Side Effects: Bendroflumethiazide may cause increases in serum uric acid, unmask diabetes, increase glycemia and glycosuria in diabetic patients and may cause hypochloremic alkalosis, hypokalemia; cramps, pruritus, paresthesias, and rashes may occur.

Supplied: Naturetin (Squibb Bendroflumethiazide) 5 mg. and 2.5 mg. tablets. Also available Naturetin c̄ K [Squibb Bendroflumethiazide (5 or 2.5 mg.) with Potassium Chloride (500 mg.)]. For full information, see Product Brief.

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'The Priceless Ingredient' of every product is the honor and integrity of its maker.

Medical Seminar

Frigidity in Women

A Symptom Not A Diagnosis

Presented as a Seminar
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PHYSICIANS ARE sometimes confronted with problems in the female patient that are not wholly attributable to an organic cause. In fact, many difficulties may be entirely psychologic and merely be manifested by organic complaints that the patient voices to her doctor. Such a conscious or unconscious attempt to avoid a discussion of the specific difficulty that she feels is paramount must show how deeply the problem troubles the patient. The physician must be astute enough to discern this type of problem and give it the attention it deserves.

Frigidity is a symptom of an underlying difficulty that may come to the attention of the physician in a number of ways. Some patients speak of it as an initial complaint. Others present various, vague organic or emotional problems as outward manifestations of this symptom. Generally, only after the doctor himself suggests this problem will the patient begin to discuss it. Many patients are reticent probably because they are ashamed or reluctant to discuss matters closely associated with sexual relations. However, the physician who is willing to spend the time and effort discussing these matters will find that many patients readily reveal their fears and anxiety about frigidity. Keeping foremost in his mind that frigidity is a symptom and not a diagnosis, the physician may then be able to make an accurate determination of the underlying cause and to suggest successful therapy.

The purpose of this paper is to discuss the definition of frigidity and its incidence, to outline a classification of the various types of frigidity, and to discuss the diagnosis, causes, and treatment of this entity. Although the specific cause of frigidity remains controversial, an understanding of the possible causes should reveal the methods of diagnosis. Even though a significant percentage of patients must be treated by psychiatrists, there are some patients with the symptom of frigidity to whom the practicing physician can offer successful diagnosis and therapy.

Incidence and Possible Mechanism

The incidence of frigidity in women has been listed by various authors[1-4] as ranging from 33 to 80%. Such a widespread discrepancy undoubtedly arises because there is no generalized agreement regarding the exact definition of frigidity in women. In animals the sexual urge is relatively easy to define because most of them exhibit the typical reaction known as "heat" or "estrus." This phenomenon is generally believed to be activated by the hormones circulating in the blood, and the willingness or unwillingness to mate in animals is controlled by these hormones. In the human, however, it seems that the sexual urge is completely independent of circulating hormones and is controlled by centers in the cerebral cortex. Mann[5] has pointed out that progesterone or estrogen, given singly or together, does not appear to change the libido of the female. Also, women who have undergone total hysterectomy and bilateral salpingo-oophorectomy or radiation of the pelvis show no predictable alteration in sex drive despite the fact that the ovaries are no longer able to produce the gonadal hormones. He suggested that the sex urge in

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humans has become independent of hormonal concentrations through the process of phylogenic development. No matter what the cause, there is no question that the sex drive in humans is much more difficult to assess than that in animals. This conclusion has a most important role in attempts to determine the incidence of frigidity.

Definitions of Frigidity

The frame of reference usually used in the definition of frigidity is the presence or absence of orgasm. Since orgasm in the female cannot be objectively measured as it can with ejaculation in the male, there is some difficulty in using this as a criterion. Two distinct types of orgasm have been postulated: clitoral and vaginal. The chief sensory region for erogenous sensation in the female is the clitoris, and it is the source of clitoral orgasm. It is supplied with a large number of genital corpuscles that are stimulated by various types of sexual activity. The female has an orgiastic center in the sacral cord that mediates the stimulation from the genitals as the impulses pass to the cortex for reception and cortical facilitation of the response. Marmor[6] discussed the presence of kinesthetic receptors within the vaginal wall that are stimulated by the erect penis and are also connected to these sacral and cerebral centers. These nerve endings are responsible for the stimulation of vaginal orgasm. Kinsey and associates,[7] however, believed that the sensory nerve supply to the vaginal lining is so meager that vaginal orgasm does not exist. Vaginal secretions during sexual activity are also believed to be objective evidence of sexual arousal.

Freud[8,9] believed that the woman's ultimate sexual response is determined by childhood experiences. He stated that several factors combine to produce the final sexual adjustment. In her earliest years a young girl is most closely attached to her mother through her dependence on the mother for feeding, warmth, and clothing. The mother also becomes the initial disciplinarian. The young girl has two sexual zones: the clitoris and the vagina. Since the clitoris is more readily accessible for attention, it is the center of childhood sexual interest. Any stimulatory activity that the child employs involving the clitoris usually brings a rapid rebuke from the mother. Repeated clitoral manipulation, which the young girl may find pleasurable, produces only more emphatic and stringent admonitions from the mother. The possible end result may be a deep resentment against the mother by the child for denying her a pleasurable activity, or it may be a deepseated inhibition for any activity associated with the genitals. As the young girl grows older, Freud believed that her attention normally turns to a closer attachment to the parent of the opposite sex, the father. She may become aware that she does not have a penis, and this may produce resentment against the male sex. All these factors combine to influence the young girl's final attitude toward sex. Freud believed that three things may happen: The young girl may acquire an aversion to sexuality, which will result in her eventual frigidity as an adult; she may refuse to accept the opposite sex, which can result in homosexuality; or she may undergo a normal transition and acquire definite interest in the opposite sex while accepting her own sex. (This form of development results in "normal" sexual adjustment.) Freud further believed that as the young girl goes through puberty her sexual interest is transferred from the clitoris to the vagina and that the sexual pleasure of clitoral orgasm in childhood is replaced by the vaginal orgasm of the "normal" adult female. It was his contention that an adult woman who does not experience vaginal orgasm is frigid.

Hitschmann and Bergler[10] also believed that the absence of vaginal orgasm is the sole criterion for determining frigidity. Although the differentiation between clitoral and vaginal orgasm may seem like splitting hairs, they believed that the clinical facts prove otherwise. They stated that the neurotic woman cannot achieve vaginal orgasm, whereas the well-adjusted woman can. They contended that clitoral orgasm is achieved only by masturbation, whereas vaginal orgasm is achieved by intercourse. Thus clitoral orgasm is an infantile act, and vaginal orgasm is an adult one.

Other authors[11-13] are not so narrow in their definition of frigidity. Most describe frigidity in terms of either the absolute or relative absence of pleasurable response to erotic stimuli. Orgasm is often used as one means of determining a pleasurable response; but, as McGuire and Steinhilber[12] pointed out, many women may gain pleasure from sexual intercourse although they do not experience an orgasm. Thus, if orgasm or the absence of it is used as the basic criterion for defining frigidity, the incidence will be much higher than a definition based on the presence of pleasurable response to erotic stimuli. Since the presence of vaginal orgasm is doubted by some and the presence of orgasm—whether vaginal or clitoral—is often hard to determine, it would seem more reasonable to define frigidity as the total or relative absence of pleasurable response to erotic stimuli.

Classification of Frigidity

There have been many suggestions for classification of frigidity. One such classification divides the various aspects into organic frigidity, true frigidity, and pseudofrigidity.

The causes for organic frigidity are easily understood. Painful intercourse due to a tight hymeneal ring, atrophic vaginitis, or other organic pathologic changes that produce dyspareunia prevent the woman from gaining pleasure from the sex act. Exhaustion due to overwork or systemic illness can make the woman reluctant to undertake relations. Impotence, premature ejaculation, or poor technique by the male partner can decrease or eliminate the pleasurable response by the female.

Rutherford and associates[13] define true frigidity as the complete and absolute absence of pleasurable response to erotic stimuli of any kind. Likewise, they define pseudofrigidity as frigidity in the individual who is capable of sexual arousal, with or without orgasm. Both classes are merely points along a spectrum of pleasurable sexual response. Thus the largest group of patients would probably be classified as pseudofrigid since they can be aroused but experience an unfilled sexual response. The evident manifestations of the pseudofrigid patient may be tension, guilt, anxiety, or multiple ill-defined physical complaints often associated with the pelvis. Weiss and English[4] more specifically list the sexual responses of the truly frigid or pseudofrigid patient as follows: (1) occasional failure to achieve orgasm; (2) only occasional orgasm; (3) mild pleasure in coitus without orgasm; (4) vaginal anesthesia, with no special aversion to coitus; (5) vaginal anesthesia with special aversion to coitus; and (6) dyspareunia and vaginismus. These responses reveal the variety of reactions that are possible in a frigid woman.

Causes of Frigidity

As was stated previously, frigidity is merely a symptom of an underlying difficulty, and so to determine the cause of the frigidity, the cause of the underlying defect must be discovered. Weiss and English[4] have provided an outline of the various psychologic causes of frigidity in the female. An understanding of these causes provides insight into the problems.

Frigidity may be caused by fear of disapproval or punishment. Many children are impressed from their very earliest years that everything associated with sex and the genitals is taboo. Parents often praise young children for demonstrating an interest in their nose, ears, hands, feet, and so forth, but sharply criticize and often discipline them when they touch their genitals. As children grow older and begin to associate with members of the opposite sex, girls are often taught that men are beasts who desire only sexual gratification. In our society, because premarital sex experience by the woman is definitely frowned upon, it is often difficult for a woman to adjust her standards to the married state. In the space of a few short minutes of a wedding ceremony, sexual activities that have been forbidden to her for years become legal and sanctioned—albeit expected. It is not difficult to understand how some women ingrained with sexual taboos all their lives fail to adjust "overnight." Young married couples who are forced to live under the same roof with parents may

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experience difficulties. The girl may fear psychologic disapproval or even bodily injury from a parent who has been adamant against her sexual activity during her single years. Her inhibitions prevent her from deriving a pleasurable response.

A young woman may have heard her mother talking about how terrible pregnancy was. Her mother may have impressed upon her the physical discomforts and pain of bearing a child. In addition, she may have impressed upon her daughter that with motherhood came the loss of whatever freedom she may have enjoyed and the addition of tedious responsibilities associated with the raising of children. It is no wonder that she gets little or no pleasure from sexual relations which could produce pregnancy.

A woman may be frigid as a conscious or unconscious manifestation of hostility toward her marital partner. Women who have often gone through an unpleasant childhood as a result of a mean or unkind father or brother find it hard to accept any man in a close relationship. Some women may unconsciously resent the domination of their lives by men. This may be a generalized resentment against the dominant positions given to all men in our society, or it may be a personalized resentment against the dominant position of a husband over a wife. Such women are frigid because they refuse to allow men to dominate them in the one area which they know is so important. The wife who feels her husband falls short of her expectations or who is maintaining an extramarital relationship may be frigid with her husband.

The female may have an underlying fear of injury to her genital organs. She may have heard how painful intercourse can be and have heard that the penis is often too large for the vagina. Such fear of pain or injury can cause her to lose all desire for an association that might bring such a result. Women may also have a fear that their participation in intercourse can cause harm to the male genitalia.

Another common unconscious cause of frigidity is conflicting loves. A woman who has had a very close attachment to her father, a brother, or an uncle may find it impossible to develop a close sexual relationship to another man. Since her ties to the father or brother have not had a sexual component, she finds it impossible to include this area in her new close relationship with a man.

One group of women never develop the emotional capacity to be able to have an intimate relationship with a person of the opposite sex. They are never able to shed the close attachment they have had to their mother—a member of the same sex—and so develop a state of latent homosexuality. These women do not find relationships with members of the opposite sex meaningful and so refuse or are reluctant to participate in such relationships.

Finally, frigidity may be caused by a feeling of self love so great that there is no room for emotional attachment to another. This condition is often seen in people who are severely neurotic or psychotic. Some women become so engrossed in their own activities, their dress, and their makeup that they do not have time to think of another person. Another manifestation of excessive self love is seen in women who devote their lives totally to their children. They see their children as a continuation of themselves and become so engrossed in their care that they have no thoughts for their own emotional relationship with their husband.

Diagnosis of Frigidity

The detection of women with underlying causes of frigidity may not be easy. The truly frigid woman who has never experienced orgasm or pleasurable sexual response will rarely come to the physician on her own. She does not know that something is lacking in her response because she has never experienced it. The husband will often bring this type of patient to the doctor. Moreover, women who do not experience orgasm, but who do derive some pleasure from sexual activity will not usually discuss the lack of orgasm as an initial complaint. Usually, it is the woman whose lack of adequate sexual response is producing marital discord who comes to the physician with complaints that relate to sexual activities.

A careful history is the cornerstone of diagnosis. Vague complaints related to the pelvis are often tip-offs to sexual difficulty. Often the patient will fail to mention sexual relations altogether. Then the doctor must inquire and attempt to determine the patient's sexual adjustment. If the patient begins to discuss the lack of pleasure associated with sex, then the physician can begin to see if he can fit the underlying cause into the scheme of etiology that has been outlined.

A complete physical examination is always necessary. Such an examination should enable the physician to pick up various causes of dyspareunia. The causes of frigidity associated with systemic disease or other organic pathologic changes should be evident. Likewise, problems associated with physical exhaustion and overwork are easily recognized.

Frigidity caused by fear of criticism or ridicule, by fear of pregnancy, or by an excessive parental conditioning on the taboos of sex may be evident after a short discussion with the patient. The other causes such as hostility toward the partner or conflicting loves usually need several sessions with a psychiatrist to become evident.

Treatment of Frigidity

Kroger[14] suggested that there are four means by which the underlying causes of frigidity may be treated.

Medical Therapy

The first can be termed medical therapy and can be carried out by any physician who makes the diagnosis of a medical cause of frigidity. A hymen can be ruptured or stretched, and vaginal atrophy or vaginitis can be treated. Kupperman[15] and Burdine and associates[1] have suggested androgen therapy in women who have difficulty experiencing orgasm. They have stated that androgen increases libido and increases the frequency of orgasm. Burdine used a long-acting parenteral androgen (Delatestryl) in doses of 200 mg. every two weeks. He emphasizes that this type of hormonal treatment is most effective when used in conjunction with psychotherapy. He stated the belief that hormonal treatments speed the results of the psychotherapy.

Superficial Psychotherapy

Kroger's second area of therapy is termed "superficial psychotherapy." Those women who have a fear of pregnancy can be helped with an explanation of the course of pregnancy, labor, and delivery. The joys of childbearing and motherhood can be emphasized. A series of discussions gives the patient time to readjust her thinking and become emotionally acceptable to pregnancy and motherhood. During this period of readjustment, adequate birth control measures can be prescribed. Clumsy or inept technique on the part of the male partner can be remedied by discussions with the husband. If a young married couple is living with parents and this proximity seems to be the cause of the wife's symptoms, the physician can call this to their attention and encourage a move. Thus the various areas of mild emotional disturbances that produce symptoms of frigidity are amenable to treatment by the practicing physician.

Psychiatric Therapy

The more deep-seated causes for frigidity must be reserved for treatment by the psychiatrist. The physician who realizes these deep emotional conflicts must convince the patient that psychotherapy is the treatment of choice. The methods of treatment range from hypnotherapy and electric shock to psychoanalysis. Although these methods are not in the realm of this discussion, it must be remembered that these treatments, of necessity, will take time because the causes are deepseated.

Prophylactic Therapy

Finally, the most successful form of therapy is prophylactic: prevent the condition before it occurs. From the very earliest ages, the parents must attempt to assume reasonable attitudes toward sex with their children. They should attempt to show that sex in its various aspects is a normal function of the human organism. The subject should not be overemphasized or strictly forbidden for dis-

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cussion but rather approached in a logical manner, similar to other areas of childhood instruction.

Kroger[14] has suggested that the following recommendations be given to parents:

1. A child's home environment should be based on love, affection, tolerance, and discipline.
2. The parents should not let the child know they were disappointed with the sex of the child.
3. The difficulties of pregnancy, labor, and delivery should never be related to the child.
4. The parents should assume reasonable attitudes toward bathing, toilet training, and childhood masturbation.
5. The father should not be seen nude by the daughter and the daughter should not observe her father in excretory activities.
6. Children should sleep in a bed alone and should not observe or overhear the parents during sexual relations.
7. The parents should give straightforward explanations of menstruation and sex at the time of puberty.
8. Parents should not overemphasize chastity to the daughter.

Virtually any physician, no matter what his field of specialization, can practice good therapy by answering a patient's questions or referring her to someone who can. The pediatrician can discuss the importance of proper sex attitudes and upbringing with parents. Premarital examinations by physicians should be encouraged. At that time, any possible organic cause of frigidity can be diagnosed and treatment instituted. A discussion of female anatomy and techniques of intercourse can alleviate much fear and concern in the young woman. Any questions that the girl may have about sexual relations can be discussed frankly.

Conclusions

Frigidity is a symptom of an underlying disorder that can be prevented by a reasonable attitude toward sexual matters by parents. Premarital examination can reveal any organic or mild emotional difficulties that could cause a lack of sexual response in a woman. Deepseated emotional problems such as hostility toward the marital partner or conflicting loves must be diagnosed by the psychiatrist who can then carry out the appropriate treatment.

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Derivatively Speaking

Strabismus — from Greek *strabos* (squinting)

Clinical Path Conference

Differential Diagnosis of a Case of Violent Behavior and Papilledema[*]

An Example of Increased Intracranial Pressure Without Early Localization

"A Case of Violent Behavior and Papilledema"

History

A forty-three-year-old farmer was admitted to the hospital after threatening his wife with a butcher knife.

The patient, who was a good historian, complained to the psychiatrist of throbbing headache, a loss of balance over four to five months, and a tendency to fall to the right. His eye grounds were examined, and he was sent to the Neurology Service.

Additional history obtained included: multiple childhood ear infections; hemorrhage from the right ear while flying in 1942 and diminished hearing in the ear since; the fact that his headache was worse in the morning and sometimes accompanied by nausea. He denied vomiting, vertigo, seizures, blackout spells, weakness, lethargy, or change in his mental ability.

He stated that he was hypersensitive but denied other illness, operations and allergies. He had one cerebral-palsied child but no other suggestive family history. No family member shared his affliction. He had not smoked in three months and denied excessive alcoholic intake.

Physical Examination

The temperature was 98.8 F, the pulse 80, the respirations 18 and the blood pressure 130/80. Examination revealed a left-handed forty-three-year-old man who appeared his stated age.

Positive physical findings were limited to the neurologic examination except for a perforated drum on the right with visible ossicles. His mental status was normal except for a tendency to project his troubles onto his wife. His station was normal with a negative Romberg. He tended to walk to the right with his eyes closed, and fall to the right with tandem walking. Finger-to-nose, heel-to-shin, and rapid alternating movements were performed well. There was no sensory deficit or motor weakness, and his reflexes were equal and active with downgoing toes. He was anosmic.[**] There was bilateral papilledema, but his fields were full and his pupils were equal and reacted well. He had nystagmus on lateral gaze, particularly to the left, and his extraocular movements were intact. Hearing was diminished on the right, with bone conduction greater than air.

Laboratory Findings

The hematocrit was 49 vol.%, the white cell count was 10,300 with 65% neutrophils, 24% lymphocytes, 10% monocytes and 1% eosinophils. The urinalysis was unremarkable, the serology negative, the fasting glucose 90 mg.% and the urea nitrogen 19 mg.%.

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[*] This presentation is based on a Neurology-Neurosurgery Clinicopathological Conference held at the State University of New York Upstate Medical Center on May 13, 1966.

[**] See Test Your Word Score Page 1855.

Continued

The chest x-ray was unremarkable, a skull series revealed a large sella turcica, and tomograms were made of that area. A mercury brain scan was negative. A closed lumbar puncture revealed an opening pressure of 350 mm. and a closing pressure of 250 mm. after 5 cc. of cerebrospinal fluid were removed. There were no cells, the fluid was clear and colorless, the total protein was 250 mg.% and the colloidal gold 55544332211.

Hospital Course

On the 19th hospital day, the patient was noted to have weakness in his right arm and a diminution of graphesthesia.* He was seen by a neurosurgical consultant, who obtained the following additional history: For 10 years he had had bifrontal headaches and some nausea, and although he rarely vomited, this always relieved the headache. For five years he had noted a pulsatile noise in both ears. For three to four years he had been forced to urinate each time he put his hands in water. He had been unable to smell for one year and had noted blurred vision bilaterally accompanying his headaches for one year.

On the 25th hospital day bilateral parieto-occipital burr holes and a right brachial angiogram were performed. The ventricles were noted to be enlarged. On the 27th day a ventriculogram and a pneumoencephalogram were performed. The ventricular fluid had a protein of 3 mg.%.

The following day the patient became acutely apneic. Mouth-to-mouth respiration, endotracheal tube, respirator and ventriculostomy, and eventually tracheostomy were all required to revive him. The ventricular pressure remained high, and on the 32nd day a Spitz valve was inserted, following which he became very alert, although unable to take oral feedings.

From the 33rd to the 40th day the patient gradually deteriorated with development of fever, polyuria, hypernatremia (Na 170 meq/liter) and azotemia (BUN 146 mg.%). These conditions were largely corrected by cessation of hypertonic tube feedings and rehydration, but the valve appeared to be functioning poorly. The ventricular pressure on the 40th day was 300 mm. and the valve was replaced. The protein in the ventricular fluid was 78 mg.%.

On the 70th hospital day a peri-urethral abscess forced withdrawal of the Foley catheter, and after an initial drop in temperature, he became febrile at 103° F, then became shocky and died while being treated with antibiotics, steroids and vasopressors on the 72nd hospital day.

An autopsy was performed.

Roentgen Interpretation

Dr. Alfred S. Berne:**

Plain films of the skull (Figure 1) reveal that the superior portion of the right petrous pyramid is ill-defined, especially in the region of the internal auditory canal. The detail is not optimal and a prominent condyloid foramen in the occipital bone partially overlies the internal auditory canal. However, there is suspicion of erosion of the right internal auditory canal.

A right brachial angiogram was performed (Figures 2-a and 2-b) and these films demonstrate evidence of dilated lateral ventricles. The anterior cerebral arteries are bowed and the thalamostriate vein on the right is convex laterally, indicating moderate to marked lateral ventricular enlargement. A specific diagnosis as to the etiology of the dilatation of the ventricles cannot be made from the angiogram.

A ventriculogram was performed (Figure 3) and demonstrates moderate to marked symmetrical dilatation of the lateral ventricle. The aqueduct of Sylvius is slightly dilated and is displaced to the left. The fourth ventricle is rotated and displaced to the left.

These films demonstrate an obstructive hydrocephalus due to a mass lesion on the right side in the posterior fossa. There is suggestion of

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*See Test Your Word Score Page 1855.

**Chief, Department of Radiology Memorial Hospital, Syracuse, New York.

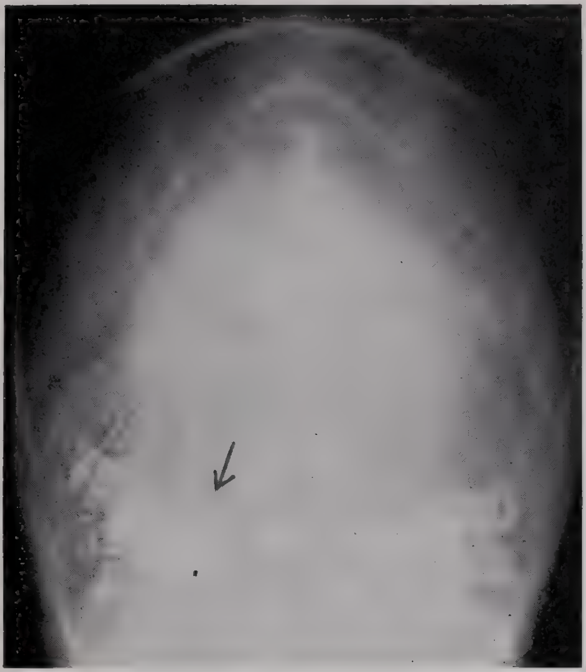

Fig. 1 — Towne view of the skull. The right internal auditory canal appears ill-defined and the porus appears enlarged.

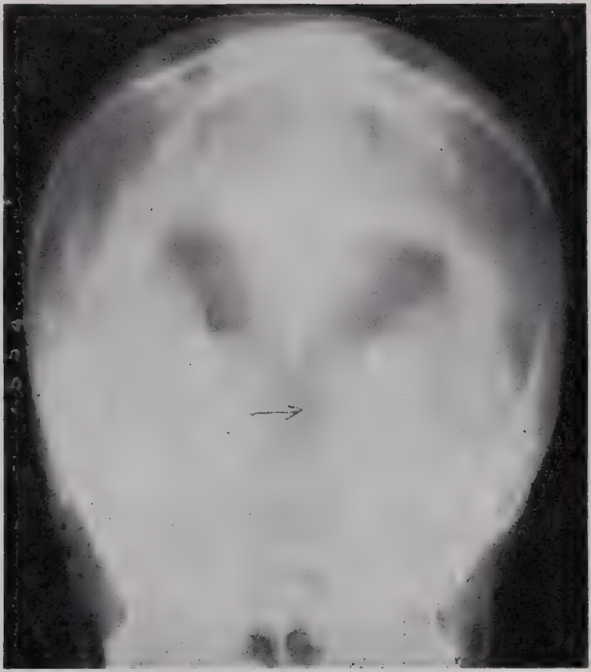

Fig. 3 — A reverse Towne view made during ventriculography demonstrating symmetrical marked hydrocephalus. The displacement of the aqueduct of Sylvius and fourth ventricle from the right to the left is seen.

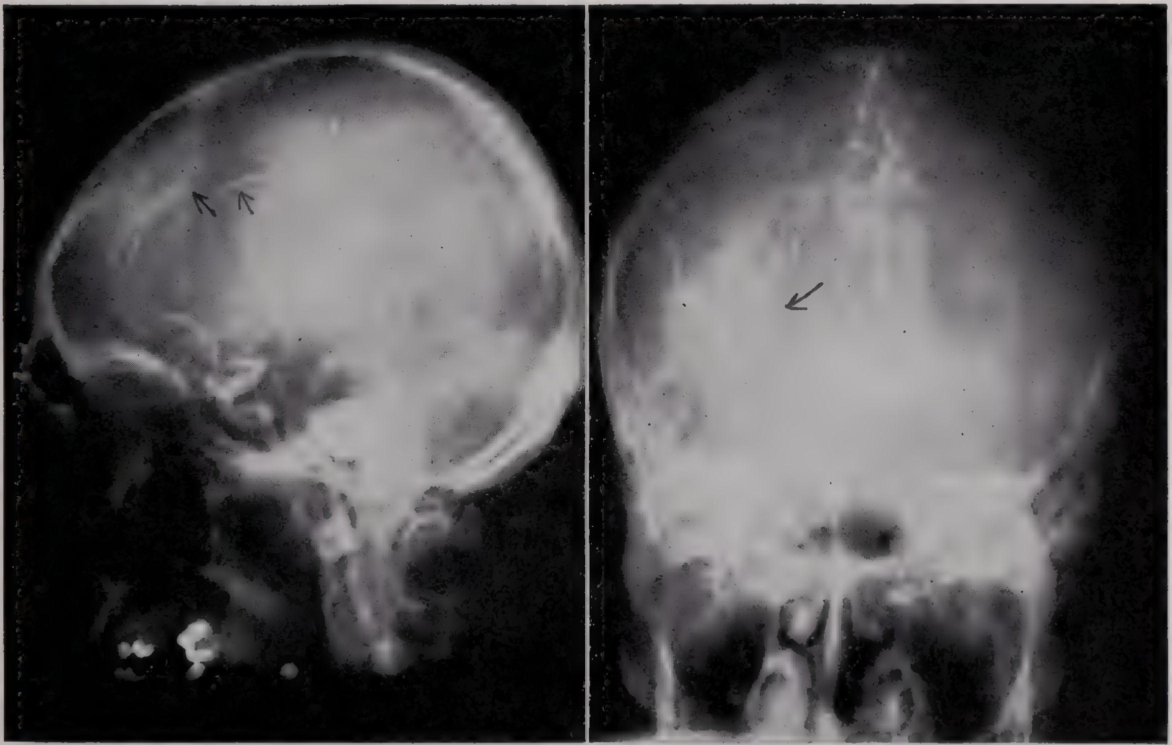

Fig. 2-a (left) and 2-b (right) — Lateral brachial angiogram and frontal brachial angiogram, arterial and venous phase respectively. The angiographic manifestations of dilatation of the lateral ventricles are seen. The thalamostriate vein is bowed laterally and there is bowing of the anterior cerebral arteries in the lateral view.

Continued

rotation of the fourth ventricle, and the change in the vicinity of the internal auditory canal together with this suggests that an extra-axial lesion in the posterior fossa on the right is causing the hydrocephalus. The diagnosis would be more definitive if the visualization of the internal auditory canal on the right side was of better quality or perhaps tomographic.

The other possibility would be an intra-axial mass on the right side; but in the lateral view there is no real kink at the junction of the third ventricle and the aqueduct.

Overview

Dr. Arthur Ecker:*

Without early localizing neurologic symptoms, this 43-year-old man presented with longstanding, progressive, increased intracranial pressure, ending in apnea, coma and death. This is an important practical problem, because the patient may have had a curable lesion.

For ten years the patient had had bifrontal headache with nausea, worse in the morning, and relief after vomiting. Early morning headache is often a clue to increased intracranial pressure. For five years the patient had heard a pulsatile noise in both ears. It is not stated whether others heard this or not. This is suggestive of an arterial bruit. If it cannot be heard by auscultation of the neck or head, sometimes its relationship to the pulse can be determined by the patient's beating with his hand in time with what he hears while the physician takes his pulse. For one year the patient had had blurred vision with headaches. This suggests failing compensation of increased intracranial pressure. The only symptom of papilledema is transitory blurring of vision. For four or five months there had been loss of balance.

Examination revealed bilateral papilledema. There is no mention of hemorrhage or exudates and presumably this papilledema is of the chronic type. A large sella turcica is reported. This suggests a slow process with reossification such as might occur with an intrasellar lesion, suprasellar lesion — such as craniopharyngioma,** or the dilated third ventricle of obstructive hydrocephalus. Less commonly an arterial aneurysm of an internal carotid artery or, rarely, one of the terminal portion of the basilar artery may produce enlargement of the sella. The lumbar puncture pressure was recorded at 350 mm. of water and the total protein content of the lumbar fluid was 250 mg. %.

On the day after the ventriculogram and pneumoencephalogram, there developed acute apnea and coma, a not uncommon complication of ventricular obstruction, usually ascribable to shifts in intracranial tissues. These include transtentorial movements of the brain stem up or down at the tentorial notch, buckling of the brain stem and secondary obstruction of cerebrospinal fluid pathways at the tentorial notch from herniation of temporal lobe or cerebellar tissue. There may be traction on the branches of the basilar artery. The result of these processes leads to hemorrhages in the brain stem and death. For these reasons the edges of the tentorium at the notch, in cases of increased intracranial pressure, can be called "the jaws of death." Furthermore, there may have been herniation of the cerebellar tonsils into the foramen magnum. In short, this is a case of progressive, increased intracranial pressure without early localizing neurological symptoms.

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**See Test Your Word Score Page 1855.

Special Features of This Case

Protein Content of Cerebrospinal Fluid

The total protein content of the lumbar fluid was 250 mgm.% at first and later 480 mgm.%. (On the contrary, the ventricular fluid at first contained 3 mgm.% of total protein, but after the valve was inserted, 78 mgm.%). This high protein content is a most valuable sign, suggesting that the lesion is in contact with fluid continuous with the lumbar fluid. It could be anywhere in the cranial or spinal subarachnoid spaces. However, it apparently was blocked — at least from the lateral ventricle sampled, where the protein content of the fluid was normal at first.

The mechanism of increased protein content of the lumbar fluid is unknown, but it has been suggested that tumors of the cerebellopontine angle act like spinal cord tumors, blocking the subarachnoid pathways. The protein content may be related to the vascularity of the tumor with back-pressure in the veins, to brain edema, to the rate of growth, to the shifting of the medullary axis or to breakdown of degenerative products of the tumor itself.

In the Journal, BRAIN, in 1952, Stern reported two of five posterior fossa meningiomas to have a total protein content of over 200 mgm. %. However, with meningiomas in general, in only 12% is the total protein over 200 mgm.%. Geoffrey Jefferson described three cases of cerebellar hemangiomas, in each of which the cerebrospinal protein content was over 500 mgm.%. Nevertheless, by and large, a high protein content in a case of increased intracranial pressure suggests primarily an acoustic nerve tumor. In a published series of these the protein content was over 50 mgm.% in 97% of the cases and over 200 mgm.% in 45% of the cases.

Cerebrospinal Fluid Pressure

The original pressure of the lumbar fluid was 350 mm. of water. After 5 cc. were removed the final pressure was 250 mm. The Ayala index* (final pressure divided by original pressure times amount removed) was 3.6. This is a low reading, well below the normal of 5.5. It suggests a diminished reservoir of cerebrospinal fluid, connected with the lumbar space. Therefore, this is *not* a case of communicating hydrocephalus with dilated ventricles. This conclusion is confirmed by the discrepancy between the protein content of the spinal fluid and that of the ventricular fluid. We therefore must seek an intracranial mass — such as a neoplasm, abscess or aneurysm — rather than simply blockage of the subarachnoid pathways.

Forced Urination

The patient was forced to urinate each time his hands were placed in water. Could this be a form of reflex epilepsy? No associated loss of awareness is mentioned. I was unable to find a case of forced urination as a sign of focal epilepsy in the literature. Nevertheless, the paper of Andrew, Nathan and Spanos, in the Journal of Neurosurgery for 1966,

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*See Test Your Word Score Page 1855.

describing disturbances of micturition from lesions in the superior frontal convolution or the septal region (gray matter abutting the lamina terminalis and anterior commissure) suggests that such cases may some day be described. Penfield and Kristiansen described urinary incontinence in a number of cases of focal epilepsy, but this always occurred late in an attack or immediately after it. There was one patient with an urge to void who had microgyria* in the left frontal region. There was a single patient who had involuntary voiding as part of a minor seizure but none where it was precipitated by placing the hands in water.

The Bruit

A bruit of itself means nothing. However, it does occur in time with the heartbeat in cases of increased intracranial pressure in children. It is also present in arteriovenous fistulae. Occasionally it appears with a very vascular tumor — such as meningioma, glioma or tumor of the glomus jugulare and, uncommonly, with an arterial aneurysm. In describing nine cases of arteriovenous malformations in the posterior fossa, Olivecroner did not mention the presence of the bruit.

Localization in Cerebral Hemispheres?

There are a few clues that might suggest a supratentorial mass.

Psychiatric Aspects

Just before admission to the hospital the patient projected his troubles on to his wife and threatened her with a butcher knife. Does this point to a lesion in the frontal lobe? The presence of a psychiatric disorder can be ascribed to organic disease of the brain, but the nature and content of the psychiatric disorder depend not on the parts of the brain affected but on the background and nature of the patient. This was a late symptom in this patient who was mentally alert and a good historian. The alertness and good memory speak against a rapidly growing glioma or metastasis in the cerebral white matter.

Mercury Brain Scan

A mercury brain scan was reported negative. Such a scan is said to be positive in 85% of the large hemispheral tumors but misses most of the astrocytomas. It does recognize a small number of cerebellar tumors but misses most of the small deep tumors of the brain stem. Even if read promptly, a small arteriovenous malformation may be missed.

Anosmia

Bilateral anosmia was present for one year. Could this be an olfactory groove meningioma extending up into the frontal lobes? In 15 of Cushing's 29 cases of olfactory groove meningioma, anosmia was absent. However, choking of the optic disks with normal vision is rare in such cases, since optic atrophy occurs early. No local x-ray changes were described.

A suprasellar meningioma extending forward to the olfactory nerves is possible, but again, in these cases, blindness and optic atrophy come first and there is rarely papilledema. A primary tumor of the falx with direct pressure blocking the third ventricle or foramen of Monro can produce bilateral anosmia.

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*See Test Your Word Score Page 1855.

We can conclude that in this case bilateral anosmia is likely to be a late sign of increased intracranial pressure and not of localizing value. For example, in Cushing's series of acoustic nerve tumors, anosmia was present in 17% of the cases. However, in the recent series of cases of acoustic nerve tumor, anosmia has been described in only 2 to 5% of the cases.

Lesions of the Third Ventricle

There was no postural effect on the headache, as in colloid cyst and other lesions of the third ventricle. There was no local visual or endocrine signs, no polyuria, polydypsia, or evidence of pituitary insufficiency.

Frontal Lobe

In frontal lobe tumors there may be incoordination and ataxia as well as increased intracranial pressure. However, a tumor arising in the frontal lobes or corpus callosum is likely to cause mental changes early. The absence of convulsive seizures and localizing defects point away from the sensorimotor cortex.

Posterior Fossa

As Jefferson has pointed out, there is an old neurological dilemma: in a patient with clear evidence of tumor is the lesion above or below the tentorium? There is often difficulty in discriminating between ataxia of cerebral or cerebellar origin. The issue will frequently be solved by special examinations. Even so, the preoperative diagnosis will often be one of probability rather than certainty.

Electroencephalography in Posterior Fossa Lesions

In the presence of papilledema a normal electroencephalogram is in favor of a posterior fossa tumor. This applies to most acoustic nerve tumors and metastases in the posterior fossa. Occasionally, in a large tumor of the posterior fossa, with distortion or involvement of the brain stem, there are bilateral slow waves — usually fairly rhythmic and regular — but never sharp waves, spikes or abnormal complexes (Pampiglione, 1953).

Ataxia

For four or five months the patient had loss of balance with a tendency to fall to the right. This was confirmed on examination when he walked to the right on tandem walking or with eyes closed. It was further confirmed by the observation that the direction of the slow component of the nystagmus was toward the right side. Nystagmus was marked — especially when the patient looked to the left side (corresponding to the quick component).

Unfortunately, caloric tests were not carried out, presumably because of the perforated eardrum. However, in such cases otologists are beginning to perform caloric tests with a sterile saline solution to which antibiotics have been added.

Continued

Otogenic Lesions

This patient had multiple childhood ear infections and a hemorrhage from the right ear while flying in 1942. He also had pulsatile noises in both ears and impaired hearing on the right.

If he had had a cholesteatoma in the middle ear (which extended into the dura) this should have been visible in the plain films of the skull. He could have had a chronic brain abscess with cerebellar signs, as this can occur even without increase of cells or protein in the cerebrospinal fluid. It is also possible that arachnoiditis in the cerebellopontine angle could have produced this clinical picture.

In the later part of the hospital course there was weakness of the right arm and diminution of graphesthesia (presumably in the right upper limb). These signs probably resulted from compression of the left cerebral peduncle against the sharp edge of the tentorium, having been displaced by a mass from the right side in the region of the tentorial notch. They are less likely to have resulted from extension of a left frontal mass, where one would have expected some facial weakness first. Weakness of a limb occurs as a late sign in about 5% of posterior fossa tumors.

Non-Neoplastic Infratentorial Lesions

One must consider Arnold-Chiari malformation, but this presents as increased intracranial pressure primarily in the age group 15 to 25 years, and there are usually x-ray changes in the region of the foramen magnum and upper cervical spine. Aqueductal stenosis can occur at any age but particularly in the younger group. In basilar meningitis with communicating hydrocephalus there would not be the gross discrepancy between ventricular and spinal fluid protein. Furthermore, the Ayala index would be high rather than low. Ependymitis with blockage of the foramina of Magendie and Luschka and a dilated fourth ventricle or a cyst through the tentorial notch — perhaps from a lateral ventricle — are likely to occur in younger people.

Diffuse Hypertrophy of the Cerebellar Cortex

In 1955 Oppenheimer summarized eleven cases from the literature in which there was a progressively enlarging mass in the cerebellum. There were grossly expanded folia but there was no definite neoplastic mass. Microscopically there were atypical nerve cells, a reduction of central white matter and absence of recognized granule and Purkinje cells. One case history lasted ten years. The spinal fluid protein was described in two of these cases and was not higher than 55 mgm.%.

Ischemic Edema of the Cerebellum

This occurs usually in older people with arteriosclerosis. It is not associated with chronic symptoms but may simulate a malignant cerebellar tumor.

Infratentorial Tumors

The ataxic gait for four or five months strongly points to a posterior fossa lesion.

Jefferson's experience with posterior fossa tumors in the fifth decade of life included forty-eight cases of acoustic nerve tumors, fifteen hemangiomas, seven astrocytomas, and seven metastatic lesions.

Intra-axial Tumors

Could this be a lesion of the mid-brain? There was no disturbance of the pupils and none of the extra-ocular movements. Could it be a pontine glioma? There were no other cranial nerve palsies and the spinal fluid protein was high.

Intraventricular Tumors

Could this be a lesion of the fourth ventricle with invasion of the dentate nucleus or peduncles? There was no nuchal rigidity with retraction of the head and no rise in ventricular protein. These tumors may also be associated with cranial nerve palsies.

Extra-Axial Infratentorial Tumors

Usually with meningiomas of the tentorial notch there is increased intracranial pressure with headache and vomiting. The symptoms may last up to fifteen years. Nevertheless, two thirds of the cases of meningiomas have symptoms of three years or less. There may be disorder of balance and other cerebellar signs, nystagmus, stiff neck and hyperreflexia. Occasionally there are diminished hearing, changes on caloric testing, and fifth nerve involvement. Meningiomas of the convexity of the cerebellum appear primarily as increased intracranial pressure without localizing signs. Most cases of meningioma of the posterior fossa have a low protein content of cerebrospinal fluid. The differential diagnosis depends on special studies, especially pneumoencephalograms and vertebral angiograms.

Hemangiomas

The history is usually under two years in these tumors of the cerebellar hemisphere. They occur in the age group 20 to 50 and are more common in men than women. Cerebellar disturbances of gait and station are common, along with nystagmus.

Posterior Fossa Dermoid Cysts

These tumors usually present with the clinical picture of vascular accident or sub-acute meningitis, but a clue may be oily cerebrospinal fluid containing cholesterol. Rarely, the symptoms and signs are those of progressive internal hydrocephalus without symptoms of meningitis. These tumors lie in the midline and have an extremely slow evolution of symptoms. X-rays may reveal abnormalities of the cervical spine, associated with truncal ataxia without incoordination of the limbs.

An Aneurysm of the Basilar Artery appeared in the cerebellopontine angle and gave all the symptoms typical of an eighth nerve tumor, including a high protein content of the spinal fluid, enlargement of the internal auditory canal, progressive deafness and tinnitus.

A Neurinoma of the Fifth Nerve arising from the Gasserian ganglion and extending down through the tentorial notch is usually recognized by an enlargement of the foramen ovale and/or the foramen rotundum.

Continued

Usually there is some atypical trigeminal pain or paresthesia and it is said that there is always corneal anesthesia. These cases may be associated with a high protein content of the cerebrospinal fluid.

Tumors of the Glomus Jugulare arising in the dome of the jugular bulb may appear as a polyp in the external auditory canal. Its intracranial extension may be marked by deafness, tinnitus, vertigo and otorrhea. There may also be involvement of the sixth or seventh nerves as well as dysphonia and dysphagia. The x-rays usually reveal bony defects.

Ependymomas of the Cerebellopontine Angle are rare tumors which arise within the lateral recess of the fourth ventricle and emerge from the foramen of Luschka. Clinically they may be indistinguishable from other masses in the angle. However, in one personal case there was involvement of the ninth and twelfth cranial nerves with sparing of the fifth, seventh, and eighth.

Acoustic Nerve Tumor

As indicated by Jefferson, in middle age the most common tumor of the posterior fossa is an eighth nerve tumor. This is a benign tumor which must be considered pre-eminently in differential diagnosis. Commonly there is headache which may be frontal. One must be especially cautious not to ascribe eighth nerve symptoms to pre-existing ear disease, when

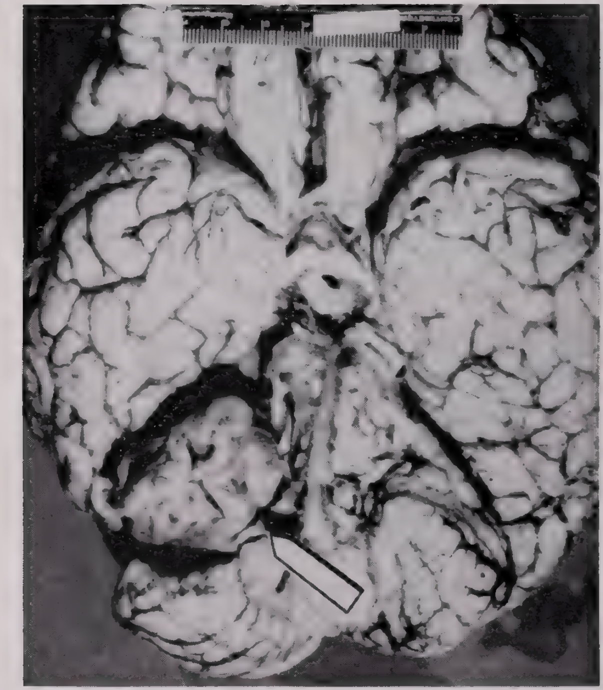

Fig. 4 — Base of brain with right acoustic neurinoma *in situ.*

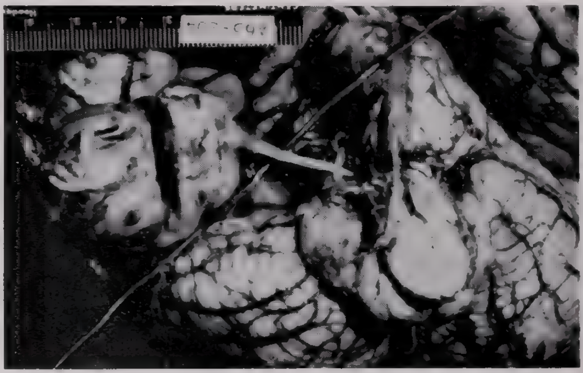

Fig. 5 — Tumor arising from eighth nerve, displaced from its bed.

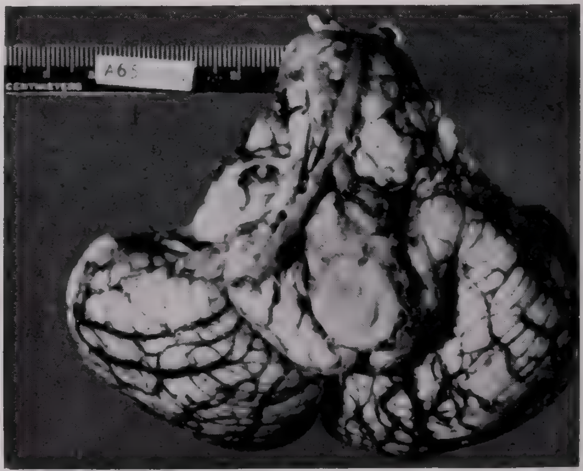

Fig. 6 — Bed of tumor in brain stem and lateral lobe of cerebellum. Extreme herniation of cerebellar tonsils.

there is evidence of increased intracranial pressure. The history of former ear disease may prove to be seriously misleading. Characteristically, cerebellar signs in eighth nerve tumors affect gait and produce nystagmus with a rapid phase to the opposite side.

The cerebrospinal fluid pressure was elevated in 60% of the cases of Pool and Pava, and the protein content was over 50 mgm. in 97% of the cases and over 200 mgm. in 45% of the cases. Of all brain tumors the acoustic nerve tumor is most prone to have an elevation of the total protein content of the cerebrospinal fluid.

Concerning the long history, ten of Pool and Pava's 122 cases had unilateral hearing difficulty for 10 to 25 years. Headache from one to ten years was characteristic. The erosion of the porus acousticus occurs in only about 60% of the cases, and one must not be misled by normal plain skull films.

Summary

This is a 43-year-old man with 10 years of bifrontal headaches, five years of a pulsatile noise in both ears, one year of blurred vision, four months of loss of balance where examination revealed bilateral papille-

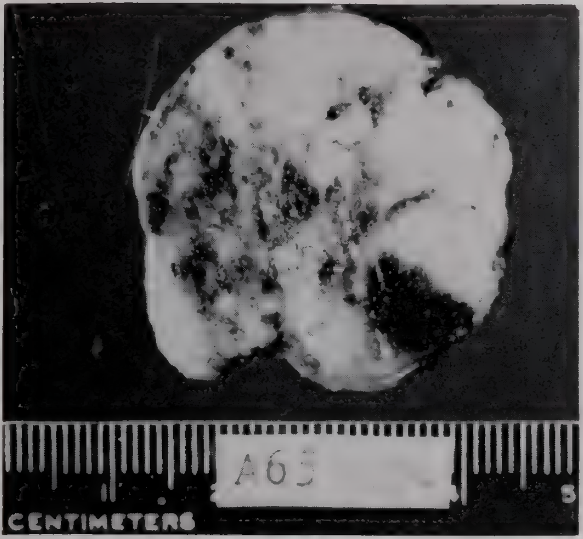

Fig. 7 — Section through tumor showing hemorrhage and degeneration.

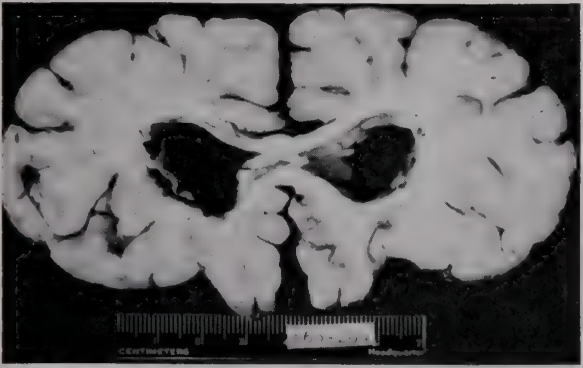

Fig. 9 — Coronal section, cerebral hemispheres, showing hydrocephalus and subependymal hemorrhage.

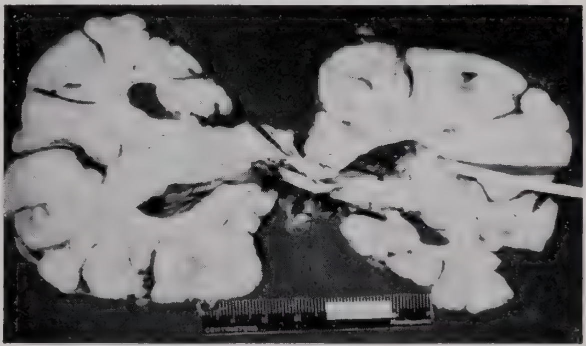

Fig. 8 — Coronal section through cerebral hemispheres with Spitz-Holter valve.

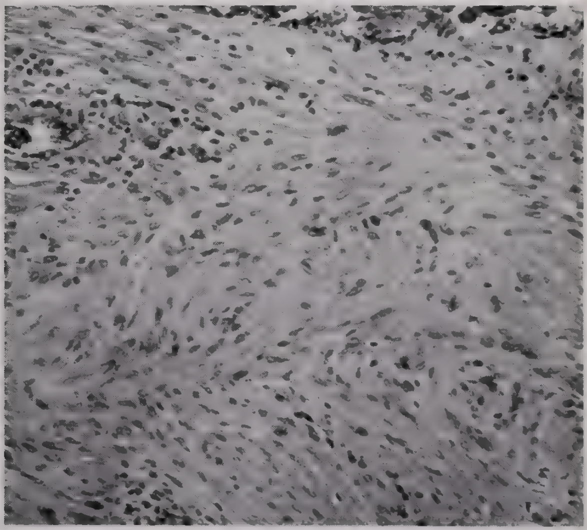

Fig. 10 — Microscopic pattern of tumor.

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dema, increased cerebrospinal fluid pressure, greatly increased cerebrospinal fluid protein content, with staggering to the right and nystagmus to the left.

The evidence is strong that this is a right-sided cerebellopontine angle tumor, most likely arising from the eighth nerve.

Pathology

Dr. J. Albert Schaefer*

Autopsy findings in this puzzling case were most interesting. Intracranially there was a large right acoustic (8th nerve) neurinoma which measured 4 × 3 × 2 cm. and lay in the classical location at the cerebellopontine angle. The tumor impinged considerably upon and indented the right cerebellar hemisphere and to a lesser extent, the pons. Figures 4, 5 and 6 show the external aspects of the tumor and its relationships to the pons and cerebellum. The cut surfaces of the tumor were pale gray to yellowish and tannish-gray and moderately firm, irregularly mottled and disrupted with reddish-brown hemorrhage and focally degenerated and softened tissue, as shown by Figure 7. Gross examination also revealed the Spitz valve in place, and there was moderate hydrocephalus secondary to the extra-axial tumor mass compressing the brain stem and compromising the aqueduct of Sylvius. There were also foci of recent and remote intracerebral hemorrhage in the left parieto-occipital region and subependymally along the left lateral ventricle, respectively, probably secondary to the increased intracranial pressure. Figures 8 and 9 show both the Spitz valve and the hydrocephalus as well as the foci of intracerebral and subependymal hemorrhage.

Microscopically the tumor showed a rather typical histologic appearance, principally of Antoni type A pattern with palisading of nuclei and occasional Verocay bodies, but also with scattered foci of Antoni type B degenerative pattern. The general microscopic pattern of the tumor is shown in Figure 10.

The cause of death in this interesting case of cerebellopontine angle tumor was sepsis, supported morphologically at autopsy by the presence of a periurethral abscess with accompanying suppurative prostatitis and cystitis, and also by acute ulcerative and hemorrhagic tracheobronchitis with retained purulent secretions, partial bronchial obstruction, and bronchopneumonia of the right lung.

Arthur Ecker, M.D.
Syracuse, New York

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Eighteenth Century English and Irish Remedies

For Smallpox: To cure the smallpox, take a bun from the shop of a person who, when she was married, did not change her name. It must not be paid for, nor must the person be thanked for it. Give it to the patient to eat, and the smallpox will be cured.*

— The Dial Press, New York, 1952, p. 149.

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*Rapport, Samuel, and Wright, Helen: Great Adventures in Medicine.

It is the customary fate of new truths to begin as heresies and to end as superstitions. — T. H. Huxley

Grand Rounds

Management of Combined Organic and Emotional Factors in a Post-Partum Psychosis

DAVID B. ROBINSON, M.D.
Syracuse, New York

Dr. David B. Robinson:*

The reasons for reporting the present unusual case of post-partum psychosis are several. The case presents a combination of toxic and emotional etiologic factors in the development of a psychotic reaction. It is believed that since both factors (psychic and somatic) were recognized in this case and treated with equal intensity, the clinical course was a dramatically favorable one. Furthermore, this case provides a backdrop for brief discussion of the development and handling of many acute psychotic reactions observed in general hospitals and therefore pertinent to a general medical audience.

Case Report

Dr. Donald T. Brooks, Jr.:**

The patient is a 25-year-old gravida IV, Para III female. Catamenia 13 × 32 × 5. She was close to her expected date of confinement.

Present Illness

Nine days prior to the present admission the patient had been referred into Syracuse Memorial Hospital from a neighboring hospital with a diagnosis of possible abdominal pregnancy or placenta praevia. Sterile pelvic examination done here at that time

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showed a large, cystic, extrauterine mass in the cul-de-sac, displacing the cervix anteriorly and superiorly behind the symphysis pubis. The cervix was closed and uneffaced. The fetus was in transverse presentation. X-rays accompanying the patient were interpreted by the Syracuse Memorial Hospital radiologist as showing an intrauterine pregnancy with transverse presentation and the presence of a soft tissue mass in the cul-de-sac, the exact nature of which could not be determined. The placenta could not be visualized. Because of the stage of gestation the patient was returned to the neighboring city hospital to be re-admitted to Syracuse Memorial Hospital after two weeks for further evaluation.

The patient had had a relatively uneventful prenatal course. Her blood pressure had remained normal and she had gained a total of 20 lbs. in weight.

Her first pregnancy had resulted in fetal demise at the sixth month of gestation. Two months after the fetal death, mild uterine contractions developed, she was hospitalized and told that she was not in labor. She was given an enema and placed upon the bed pan. While expelling the enema, the macerated, decomposing fetus was passed into the bed pan while the patient watched the entire procedure unattended and terrified. Two subsequent pregnancies were normal with spontaneous deliveries at term.

Past Medical History

Essentially negative except for a delirious episode with fever of 104° associated with bilateral otitis media at age 19. The patient had had psoriasis for the past ten years with alternating remissions and exacerbations.

Family History

Patient's mother died at age 49 of cancer of the uterus. Father died at age 51 of coronary artery disease. No other familial diseases.

Social History

The patient has been married for seven years. She revealed no unusual habits, does not use drugs, narcotics, or alcohol to excess.

Physical Examination

The significant physical findings on admission included: BP of 120/80, psoriasis of the legs, arms, abdomen, chest and back. There were no abnormalities of the heart or lungs. The abdomen showed the fundus to be approximately 30 cm. with caliper measurements. The fetus appeared to be in a transverse presentation with the fetal heart heard in the right upper quadrant. A sterile pelvic examination done in the morning following admission showed no change in condition except that the fetus was now in breech presentation.

Laboratory Data

On admission: Hgb. 10.4 gm.%; hematocrit 36 vol.%; wbc 9,000; urinalysis — negative.

It was decided that with the fetus at term and with a large obstructing mass in the pelvis completely displacing the cervix, delivery would best be accomplished by cesarean section with exploration of the pelvis and removal of the mass if feasible. A laparo-trachelotomy was performed under local anesthesia, and a 6 lb. 14 oz. infant was delivered which breathed and cried spontaneously. Following repair of the uterine incision, a large, right ovarian cyst (12 × 14 cm.) was found to be completely replacing the right ovary. The cyst was removed and the abdomen was closed in routine fashion.

The patient ran a completely normal postoperative course until the fourth postoperative day when her temperature spiked to 100.4°. On the sixth postoperative day the temperature again rose to 100° on two occasions. On the seventh postoperative day she had a slight chill which she did not report to the nursing staff at the time. On the morning of the eighth day the patient was told by the pediatrician that the baby had a congenital heart anomaly, the exact nature or seriousness of which had not yet been determined. Two hours later the patient had a shaking chill and her temperature spiked to 103.8°. She was seen promptly by a member of the house staff who, upon palpating her abdomen, asked, "Does it hurt?" Shortly thereafter the patient became deliriously maniacal, reiterating the phrase she had just heard, "Does it hurt?" She thrashed wildly in bed and screamed that she was about to die. She could not identify those around her. She said that while at the previous hospital God told her in a dream that she was going to die. She pleaded with the attendants to believe her and shouted that she knew we wouldn't believe her. She alternated quickly between extreme moods of excitement and depression. She told the doctors not to try to calm her and not to tell her that she was all right because she knew that she was going to die. She wanted messages given to her husband and then she said not to tell her husband that she was going to die for that would make him feel very bad. She thrashed, screamed and kicked out at the various attendants. At times her sentences were completely incoherent and she seemed to be out of contact with those around her. She also said that "they" were in contact with her and told her "many things." Who "they" were remained obscure, but she was evidently referring to hallucinations. On one occasion she appeared to be subjectively experiencing precipitous delivery. She called out — "Here it comes! The head's being born now!"

Attempts at quieting and reasoning with the patient were completely unsuccessful. She was given promazine hydrochloride* 100 mg. I.V. and 100 mg. I.M. which she resisted, accusing the staff of trying to kill her. The Psychiatry Department was notified and immediately a member of the staff came to see her.

Dr. Robinson:

When I arrived the patient was lying quietly in bed with an aide sitting expectantly in a chair facing her from a position near the foot of the bed. The frightened roommate had left the room and had precipitously decided to leave the hospital. An atmosphere of anxiety, fear, and consternation permeated not only the patient's room but also the hallway and the nurses' station where the facts relating to the sudden explosion were made known to me by the nurses — including those who had been recipients of the patient's abuse and kicks a short time earlier.

The patient was slightly flushed, perspiring and appeared somewhat dazed and frightened. After introducing myself, I said, "You've been frightened and mixed up. I want to help you with your worries and those feelings that make you afraid and confused." She immediately and correctly identified me as a psychiatrist and asked if she were crazy. I agreed that I was a psychiatrist and repeated that she had been very mixed up. (In this way I confirmed the suspicions of and aligned myself with the still functioning, healthy or observing aspect of her ego.) In the ensuing hour's interaction, certain comments of the patient were emphatically repeated by her. Other remarks assumed special significance in their context. Concurrently, I made observations on the patient's mental status. Since it is neither possible nor desirable to give a verbatim account, extracts are presented, accompanied by some of the thoughts that occurred to me as to possible meanings of her psychotic productions.

Repeated over and again by the patient with much urgency at first was: "Tell my husband — *they don't know anything here*! That's all

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that's important! I must suffer — it's terribly painful — no one knows — God tells me that I must die — It's terrible!" (This seemed to be an attempt to deny something serious about which she had a great sense of guilt and, hence, must suffer and die. Was she reacting to the knowledge of her baby's congenital heart disease? This was the information she had learned for the first time that morning preceding the psychotic break. It is known that mothers often react to defects in their babies with much guilt,[3] feeling that they are responsible.)

The patient then identified herself with a character in a book she had read who "suffered terribly and died" despite the care of a fine doctor. I asked, "Why do you feel you must die?" She replied, "I can't tell you — I won't. When the pain is unbearable — if I say the word I won't die. But if I tell you the word, it won't work and I'll die —. I don't want to." (Here was evidence of regression to magical omnipotence and, more important, it showed the struggle of the healthy aspects of the ego to survive against the onslaught of her guilt.) "I won't tell you — I don't want my husband to be embarrassed or ashamed of me." She hallucinated actively — heard voices and ignored me. "I think it's God — Yes, it's God telling me I must die." She waved me away when I asked a question. (I felt at this point that she was retreating from me and from the observing ego. I decided to intervene in behalf of the latter.) I spoke authoritatively, "You are *not* going to die. You have a fever from an infection in your womb. The fever has you mixed up right now but you are not going to die!" She replied, "I'm not? — But then I must suffer — a terrible disease. If I could just tell you — but I can't." At this point she asked the aide and two doctors who had come in earlier to leave. She still could not bring herself to tell me the name of the disease — which proved to be "the word" she referred to earlier. I offered her paper and pencil which she accepted and then wrote the word, LEPROSY. — "Like she had in the book — it was terribly painful at the end." (The patient has had psoriasis since puberty. Such patients often have conscious or unconscious fantasies of their disease representing a punishment for evil or "sinful" deeds or thoughts. Biblical references speak of lepers as "unclean" — implying sinfulness or devilishness. Had the guilt over the imperfect child reawakened an earlier parallel sense of guilt over her psoriasis? If so, *could the concern with leprosy, i.e., psoriasis, be a screen for a less tolerable and currently more anxiety-laden concern about the defective infant?)* I decided to test this hypothesis. I told her, "You feel that you have done something terrible and deserve to suffer — something very evil." "That's right," she replied. I continued, "Perhaps you haven't — perhaps you just feel that you have. I wonder if the leprosy idea doesn't come from your psoriasis. They are totally different — leprosy is caused by a germ — something like tuberculosis — psoriasis is not. But, most important, *you feel wicked*. Why?"

At this point there was a significant transition in her. She seemed in better contact and showed more appropriate affect. "They told me I shouldn't go on the ladder." She then told of climbing a ladder during the fourth month of her pregnancy to remove plastic window screens. "They said I'd hurt myself or the baby" — (a precipitating source of the guilt?) — "but it didn't hurt — I felt no strain." Her eyes filled with tears. There were no more hallucinations after this time.

I again supported the healthy ego with tone of voice and an authoritative educational approach trying to alleviate her illogically founded guilt. "So you feel it's your fault that the baby has a defective heart. This is what you feel so guilty about. You feel that those who told you climbing the ladder would harm the baby were proven to be right. They aren't!" I then discussed prevalent folklore about congenital defects in general, and went on to discuss the known facts of congenital heart defects *in particular*, always emphasizing the absence of blame for the mother. I told her about the effects of German measles in the pregnant mother during the first trimester of pregnancy and again observed that it was not the mother's *fault* if she acquired measles at this time. Here she mused with some apparent relief, "Maybe I had German Measles."

Feeling that I should interject a positive note of hopefulness, I then discussed the difficulty of accurately assessing murmurs in the newborn and the physiologic changes in circulation from the fetal state to the neonatal period. Not wanting to foster what might turn out to be false hopes, I then talked about the marvelous advances in cardiac surgery which can now correct certain anomalies. The patient listened attentively and asked appropriate questions. Then she commented spontaneously, "I feel better. I guess I was pretty worried about this and didn't realize it." At this time she could recall my name when asked although I had inquired unsuccessfully at least five times previously during the interview. Each time I had again given her my name. By the end of the interview she was less flushed and her fever had subsided somewhat. Early in the interview she had been disoriented in time although not in place. By the end of the hour her temporal orientation was intact.

With Dr. Brooks, a program of management was then outlined to combat both toxic and emotional determinants of the psychotic reaction. Medical measures included: (1) immediate establishment of cervical drainage of the uterus; (2) simultaneous culture of uterine contents for sensitivity studies; (3) continued broad-spectrum antibiotics; (4) aspirin gr. XV, q4h; (5) force fluids; (6) temperature readings — with alcohol sponge baths for temperature elevation.

Measures were also taken to control the patient's anxiety: (1) The complete situation (medical and psychiatric) was discussed with floor nurses, nursing supervisor, OB residents and nurses' aides. (2) The husband who arrived after the storm had abated was informed in simple direct terms of the nature of his wife's reaction and the determining factors. His aid was enlisted to encourage his wife to talk freely of her feelings, particularly concerning the infant. (3) Knowing the tendency to recurrence of delirious states (especially at night) all attendants were instructed in methods of helping the patient to maintain orientation by repeated sensory contacts through visual, auditory and tactile routes. A night light was ordered for the room. The husband was requested to stay overnight since his familiar face and voice would be especially reassuring and meaningful to her in the event of a return of a clouded sensorium. (4) Oral promazine 50 mg. q4h was provided for additional control of anxiety. A tranquillizer of this nature seemed preferable to a sedative or hypnotic which might increase the clouding of consciousness. (5) The patient was to be assured insofar as possible by factual reporting concerning the status and welfare of her infant.

Continued

Dr. Brooks:

Her temperature dropped to 100.6° and then to 99.6°. However, at approximately 11:00 p.m. it again spiked to 102.6° and the patient again became delirious, uttering the same words and making the same accusations as she had previously. She was sponged and again given 100 mg. of promazine I.V. and I.M. Blood cultures were again drawn. Within a short while she quieted down and became aware of her surroundings.

The patient was kept on chloromycetin and aspirin over the next three days. The temperature never rose over 101.4° and she had no further episodes of delirium. The uterine culture showed members of the coliform group. The urine culture as well as repeated urinalyses were negative. Blood cultures failed to grow out any organisms. The wbc. never rose above 9,000. Because the temperature continued to spike to 101° at least once daily for the next three days, the antibiotics were shifted to 600,000 units of penicillin and 0.5 Gm. of streptomycin twice daily. On the twelfth postoperative day, her temperature rose for the last time. She was discharged on the fifteenth postoperative day on tetracycline 250 mg. and 200 mg. of Mol-Iron® three times a day. On discharge the hemoglobin was 9.3 Gm. %; hematocrit 32 vol %; wbc. 7,800 with a normal differential. The patient was discharged to the care of her private physician at home.

Several days after returning home a pyelitis developed with frank pus in the urine. The patient had fever to 106° for three days with no recurrence of a delirious reaction. The infant had several cyanotic episodes at home and was eventually evaluated in a medical center. Surgery was attempted but the infant unfortunately succumbed. The mother has withstood these stresses and this tragic outcome successfully without an emotional decompensation.

Discussion

Dr. Robinson:

Although the emphasis of this paper is on the psychological aspects of an illness, the obstetrical data (in the physical sense) have been reported in detail. These details convey to the reader an appreciation of the patient's preoperative stresses generally and specifically: the large number of examinations, the uncertainty, the expectant waiting, the trips to and from Syracuse, finally culminating in surgical intervention. In addition, the patient had been aware early of the possible diagnosis of abdominal pregnancy, had read about the condition and knew the serious potentiality of this condition. In the face of all of these anxiety-producing circumstances, her psychological defense mechanisms remained clinically intact until the eighth postoperative day. She had been able to relate in a friendly way to nurses, doctors and fellow patients within the hospital. She had not exhibited the schizoid, tentative modes of relating to people often apparent in the patient who is prone to develop a post-partum schizophrenic-type reaction.

The obstetrical data further provide important information in evaluating and interpreting the toxic febrile aspects of the psychotic reaction which developed. Past obstetrical history revealed an exceedingly traumatic experience related to the patient's first pregnancy. Two normal obstetrical experiences occurred subsequently. These historical data are significant in that any new life experience is approached with emotional overtones and expectancy determined by the summation of emotional responses to previous similar experiences. It is worth noting in this connection that a nurse commented spontaneously that this patient was more tense than the usual patient about receiving and expelling her preoperative enema. Otherwise she had been a "good patient." This observed response was probably conditioned by the highly traumatic experience of her first pregnancy when she expelled, unattended, a macerated, dead fetus into the bedpan following administration of an enema.

The history of a previous febrile delirious state associated with a fever of 104° suggests a lower than usual threshold for the development of a delirious reaction. Emotional factors surrounding this earlier delirious state are unknown except for the fact that at the time of the reaction she was far from home in Europe with her husband. The fact that she did not develop a delirious reaction after returning home (when her temperature rose to 106° for three successive days) again supports the hypothesis of multiple (psychologic as well as febrile-toxic) causative factors producing the psychotic reaction she experienced in the hospital.

In retrospect, it is recognized that in the face of a developing endometritis and probable incipient delirium state, the patient was presented with emotionally traumatic information about her infant. In the absence of the toxic state accompanying the endometritis, the patient's usual psychological modes of adaptation might well have permitted her to deal with the emotionally traumatic events without a psychotic break. Overwhelmed by the combination of toxic impairment of mental functioning, the summation of anxiety from events leading to surgery, and finally the emotional reactions to knowledge of the baby's abnormality, the ego gave way to explosive, psychotic expressions of affect. The language and symbols used were identical with the symbol system of dreams — namely, the language of the unconscious. In the case report presentation, an attempt has been made to translate this language in context from the manifest to the latent content. Just as the internist interprets manifest shadows on an x-ray film, the psychiatrist finds hidden meanings in dreams or psychotic productions. It is postulated that this patient's psychotic state was brought to a rapid resolution by re-establishing lines of communication and dealing directly with the latent content of her words and actions. This in turn permitted constructive handling of the immediate sources of her overwhelming anxiety and guilt. As soon as the anxiety and guilt were allayed, the psychosis subsided. The participating roles of medication are recognized. The aspirin helped to reduce the fever and the promazine undoubtedly added its quieting effect.

The importance of the message contained in the first delusion or hallucination in schizophrenic patients has been stressed by Beckett et al.[1] In their study it was observed that patients' nuclear conflicts were often expressed in condensed symbolic fashion. Freud[2] pointed out that dreams contain a condensation of current feelings (emotional and somatic) with feelings from the past. He observed further that in most dreams a hidden wish is expressed. Within the dream or psychotic production the psychiatrist looks for the elements of wish fulfillment. These were the main guiding principles in understanding the present patient's psychotic verbalizations. The parenthetical comments interspersed in the dialogue of the

Continued

case report demonstrate the use of these basic principles. Similarly, one can consider the possible meaning of the patient's delusional experience of the birth of a baby at the onset of her psychotic break. Does this represent the fulfillment of a wish to give birth to her baby "normally" rather than by cesarean section (abbnormally) and, by extension, to produce a "normal" rather than an "abnormal" infant? Such an explanation has the merit of fitting the overall pattern of her productions as "understood" from the same theoretical framework. Her response to the therapist's approach suggests validity of the working hypothesis.

In the classical investigations of Benedek and Rubinstein[3] the effects of monthly hormonal shifts in women were observed in the dream content. The sudden and dramatic hormonal changes following parturition may well participate in the development of untoward psychological reactions in those individuals who have a specific psychologic vulnerability. It is apparent that hormonal changes *alone* do not explain these reactions since the majority of mothers have no untoward reaction after parturition.

The rationale for the specific medical treatment of the endometritis needs no elaboration to the readers of this journal.

Measures outlined to help control the patient's anxiety warrant some further discussion, especially since they apply to reactions to many types of acute and chronic organic brain impairment. Patients who consciously or preconsciously sense impairment of their mental faculties characteristically exhibit much fear and dread. Their inability to think clearly, to orient themselves, or to remember recent events causes much consternation and anxiety. The physician who attempts to reassure the patient that "all is well" may only increase the intensity of the patient's reaction. The patient may then feel that no one else is aware of the terrible changes within him. He may also feel that he is being "protected" from a "truth" that is too terrible to be faced directly. For these reasons it is preferable to talk about the confusion directly, thus implying that it is recognized, not to be feared, and can be treated successfully.

Because of the mental impairment, it is helpful to increase the input of sensory cues which will assist the patient to remain oriented in time, place and person. The patient should be addressed by name, repeatedly told *where* he is and why, because he soon forgets. Familiar persons or objects in the room are helpful. A radio or TV set increases familiar auditory cues for orientation. (Care should be taken in appropriate selection of programs.) A room light helps for more rapid visual orientation at night when not only visual but also auditory cues are usually reduced.

Families as well as professional personnel not accustomed to dealing with psychiatric problems may become anxious, particularly when the patient's own fear and anxiety results in behavior that is disruptive to the hospital floor. Anxiety of personnel and/or family members readily feeds back to increase the patient's anxiety. For this reason, time spent allaying the anxiety of those around the delirious patient is well spent. Explanations and specific suggestions for constructive measures to both hospital personnel and family are helpful in this regard.

Summary

1. A patient with a post-partum psychosis caused by a combination of toxic and emotional factors has been presented.

2. The specific medical and psychologic treatment measures used in this case have been outlined and discussed.

3. General measures to help control anxiety in organic confusional states have been discussed.

References

1. Beckett et al.: The Significance of Exogenous Traumata in the Genesis of Schizophrenia. Psychiatry 19:137, 1956.
2. Freud, Sigmund: Interpretation of Dreams. London: George Allen & Unwin, Ltd., 1913.
3. Benedek, T. F., and Rubenstein, B. B.: The Sexual Cycle in Women: The Relation Between Ovarian Function and Psychodynamic Processes. Psychosomatic Medicine Monographs, Vol. 3, Nos. 1 & 2, Hoeber, New York, 1942.

Kartagener's Syndrome

This syndrome consists of the triad of chronic sinusitis, bronchiectasis, and situs inversus. It was first described by Kartagener who reported a group of cases in 1933. The syndrome may begin early in neonatal life. In most instances symptoms date back to childhood. Ninety per cent of cases were observed before the age of 15 years. The condition has been observed to occur in siblings and in identical twins. One hundred and five cases have been recorded in the literature (Krejci and Kleiman).

The pathogenesis of this syndrome depends upon the congenital factors of situs inversus, agenesis of sinuses, and a deformity of bronchi, as well as upon the acquired factor of upper and lower respiratory tract infection. There may be situs inversus totalis with transposition of the heart and the entire gastrointestinal tract, or there may be dextrocardia alone. Roentgenograms show agenesis of the frontal sinuses and either congenital absence or poor development of all paranasal sinuses. Nasal polyposis is frequently observed.

The cause of the bronchiectasis has given rise to considerable speculation. Its occurrence in siblings suggests a genetic predisposition. The incidence in patients with dextrocardia or transposition of the viscera is greater than among the general population. Suggested causes include (1) congenital weakness of the bronchial wall, and (2) abnormal position of the great vessels, which interferes with normal bronchial drainage. Because bronchiectasis is the greatest factor in the morbidity of this syndrome, it is important that all patients who have dextrocardia or situs inversus should have roentgenograms of the sinuses and chest and bronchograms if bronchial symptoms are present.

Intensive therapy with antibiotics is indicated for the recurrent respiratory infections. If bronchiectasis is present, resection is the procedure of choice.

Durham, Robert H. — Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

On Quaffing

It may be contrary to the laws of nature, but wild oats and old rye produce the same kind of crop. — Religious Telescope

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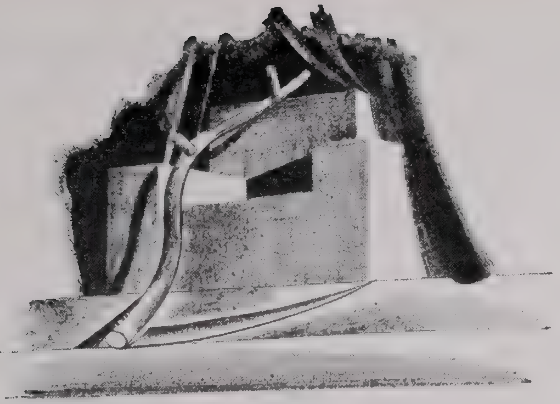

In Memoriam

Death is like thunder in two particulars: We are alarmed at the sound of it, and it is formidable only from that which preceded it. — Colton

RUDOLPH LOGEFEIL, M.D.

Dr. Rudolph C. Logefeil, 72, former chief of Staff at Fairview Hospital and medical director for the Evangelical Alliance Mission, died September 17. He was a graduate of the University of Minnesota and had done graduate and medical studies at Johns Hopkins University, Baltimore, Maryland, and Columbia University, New York.

Dr. Logefeil was a board member of the Fuller Theological Seminary and Oak Hills Fellowship, Bemidji; a member of the Hennepin County Medical Society and American Medical Association and an Associate Member of the Minnesota State Medical Association.

He is survived by his wife, two daughters and a son.

JOSEPH F. BICEK, M.D.

Dr. Joseph F. Bicek, 67, St. Paul physician and surgeon, died September 9, of injuries suffered in a fall in his home. Born in LeSueur, Dr. Bicek lived in St. Paul forty-five years.

He was a member of the Ramsey County Medical Society, Minnesota State Medical Association, American Medical Association, American College of Obstetrics and Gynecology and a fellow of the American College of Surgeons. He was a 1921 honor graduate of the University of Minnesota Medical School and a former instructor of obstetrics and gynecology at the University.

He is survived by his wife and a daughter.

WILLIAM F. MENOLD, M.D.

Dr. William F. Menold, 52, St. Paul obstetrician and gynecologist, died October 17. Born in St. Paul, he lived there all of his life.

Dr. Menold was a member of the Ramsey County Medical Society, American Board of Obstetrics and Gynecology, American Medical Association and the Minnesota State Medical Association.

He is survived by his wife, two daughters and a son.

RICHARD B. GRAVES, M.D.

Dr. Richard Graves, 58, Red Wing physician, died suddenly October 15 of a heart attack at his home in Naples, Florida. Born in Ely, Dr. Graves obtained his medical degree from the University of Minnesota.

He was a member of the Goodhue County Medical Society and the American Medical Association and an Associate Member of the Minnesota State Medical Association.

He is survived by his wife and two daughters.

FREDERICK W. BEHMLER, M.D.

Dr. Fred W. Behmler, 71, a former state senator and a practicing physician in Morris for forty years, died November 9. A native of Jordan, Dr. Behmler attended Carleton College and graduated from the University of Minnesota Medical School.

He was a former president of the Minnesota State Board of Health, former first vice-president of the Minnesota State Medical Association, and had been very active in the Boy Scouts. He was a member of the West Central Minnesota Medical Society, American Academy of General Practice, American Medical Association, and an Associate Member of the Minnesota State Medical Association. Dr. Behmler was one of the prime movers in the campaign that resulted in the establishment of the University of Minnesota, Morris, and Behmler Hall on the UMM campus was named in his honor.

He is survived by his wife, a son and a daughter. Dr. Raymond Behmler of Minneapolis is his brother.

IRWIN L. OLIVER, M.D.

Dr. Irwin L. Oliver, 62, Graceville physician, died November 21, after a lengthy illness. Born in Graceville, Dr. Oliver attended Shattuck School in Faribault and received his medical degree from the University of Illinois.

He and his father, the late Dr. C. I. Oliver, practiced together until Dr. Irwin Oliver retired in 1962 and turned the Oliver Clinic over to the City of Graceville. This father-and-son team also developed the West Central Minnesota Hospital which later was transferred to the Missionary Benedictine Sisters.

He was a member of the West Central Minnesota Medical Society, American Medical Association and the Minnesota State Medical Association.

He is survived by his wife, two daughters and two sons, one of whom is Dr. Robert I. Oliver of Jackson, Mississippi.

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Dextro-amphetamine sulfate: Excessive use by unstable individuals may result in psychological dependence.

Meprobamate: Careful supervision of dose and amounts prescribed is advised, especially for patients with known propensity for taking excessive quantities of drugs. Excessive and prolonged use in susceptible persons, e.g. alcoholics, former addicts, and other severe psychoneurotics, has been reported to result in dependence on the drug. Where excessive dosage has continued for weeks or months, reduce dosage gradually. Sudden withdrawal may precipitate recurrence of preexisting symptoms such as anxiety, anorexia, or insomnia; or withdrawal reactions such as vomiting, ataxia, tremors, muscle twitching and, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, reduce dosage and avoid operation of motor vehicles, machinery or other activity requiring alertness. Effects of excessive alcohol consumption may be increased by meprobamate. Appropriate caution is recommended with patients prone to excessive drinking. In patients prone to both petit and grand mal epilepsy meprobamate may precipitate grand mal attacks. Prescribe cautiously and in small quantities to patients with suicidal tendencies.

Side Effects: Overstimulation of the central nervous system, jitteriness and insomnia or drowsiness.

Dextro-amphetamine sulfate: Insomnia, excitability, and increased motor activity are common and ordinarily mild side effects. Confusion, anxiety, aggressiveness, increased libido, and hallucinations have also been observed, especially in mentally ill patients. Rebound fatigue and depression may follow central stimulation. Other effects may include dry mouth, anorexia, nausea, vomiting, diarrhea, and increased cardiovascular reactivity.

Meprobamate: Drowsiness may occur and can be associated with ataxia; the symptom can usually be controlled by decreasing the dose, or by concomitant administration of central stimulants. Allergic or idiosyncratic reactions: maculopapular rash, acute nonthrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever, transient leukopenia. A case of fatal bullous dermatitis, following administration of meprobamate and prednisolone, has been reported. Hypersensitivity has produced fever, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, stomatitis, proctitis (1 case), anaphylaxis, agranulocytosis and thrombocytopenic purpura, and a fatal instance of aplastic anemia, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity, usually after excessive dosage. Impairment of visual accommodation. Massive overdosage may produce drowsiness lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

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1. Schleif, R.H.: J.A.PH.A., 46:179,1957 *U.S. Pat. No. 3,062,714

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Abstracts, Briefs and Commentaries

NUTRITIONAL DEFICIT AFTER GASTRECTOMY

Weight loss is a cardinal sign of under-nutrition, and it was found that approximately 50 percent of post-gastrectomy patients suffered some degree of nutritional deficit. This was considered to be due to a number of factors, e.g., the dumping with regurgitation and vomiting, postsybal distress, and diarrhea. In addition to these, subnormal absorption through a loss of gastric reservoir, rapid intestinal transit, impaired pancreatic and biliary flow, imperfect mixing of digestive juices, and duodenal bypass were thought to be major contributing factors.

Anemia, folic-acid deficit, and post-gastrectomy bone disease were the most often encountered metabolic disturbances.

Williams suggests, as a prophylaxis for these nutritional deficits, medication containing iron salt, vitamin B12, folic acid, calcium, and vitamin D. Though this may represent some polypharmacy, such a tablet taken each night after gastrectomy should be safe, and might be expected to go a long way toward preventing deficiency states so commonly found in post-gastrectomy patients.

Carl O. Rice, M.D.
Minneapolis, Minnesota

J. Alexander Williams, Ch.M., F.R.C.S.: Partial Gastrectomy — The Late Nutritional and Metabolic Effects. Amer J Proc 17:288, 1966.

THE CHRONICALLY ISCHEMIC LOWER LIMB

The author succinctly summarizes the natural history, the diagnostic steps and the medical and surgical treatment of this disease. Careful history and examination localizes and grades the degree of ischemia.

Intermittent claudication will remain stable or improve over a five-year period in 60-90% of patients. In itself, intermittent claudication is not an indication for surgical intervention *unless* the individual cannot perform at a livelihood. Medical management must insist on abstinence from cigarettes, diligent and intelligent care of the skin of the feet and correction or treatment of other disease processes. Drugs have not proven beneficial for vasodilatation.

Ischemic rest pain, neuropathy or ischemic ulceration from slow arterial occlusion are indications for either reconstructive vascular surgery or

Continued

lumbar sympathectomy. The risk and postoperative prognosis of reconstructive surgery depend on the site of arterial occlusion. In general, the risk to life is higher, but the operative results are better for aortic-iliac disease than for femoral popliteal reconstruction. Autogenous vein grafts are favored for the latter. Lumbar sympathectomy is indicated if reconstruction is not feasible, but the results mainly affect the skin healing.

Comment: An excellent two-page summary which clearly defines the issues involved. It is a caution to the over-zealous surgeon, a comfort to the non-surgeon and an outline for those interested in patient welfare.

Jerome T. Grismer, M.D.
Minneapolis, Minnesota

Schatz, I. J.: The Chronically Ischemic Lower Limb. JAMA 197:915, 1966.

THE USE OF CORTICOSTEROIDS IN THE TREATMENT OF RESPIRATORY FAILURE ASSOCIATED WITH MASSIVE FAT EMBOLISM

It is estimated that fat embolism carries an overall mortality rate of 10-20 per cent. Typically, respiratory and neurologic symptoms appear two to three days after injury. Following an initial clear interval, signs of delirium, restlessness, and mild tachypnea are noticed. These symptoms and signs may clear spontaneously, but frequently, severe hypoxemia, respiratory and metabolic acidosis, coma, and death ensue. These patients die of respiratory failure.

The authors present the cases of three patients with fat embolism. One died and two recovered; the two patients who recovered had been treated with parenteral cortisone. In one, recovery occurred from a moribund state; in the other it was felt that cortisone prevented acute respiratory failure.

The etiology of fat embolism is poorly understood. The principal theories regarding the production of fat emboli are the mechanical theory proposed by Gauss and the biochemical theory advanced by Lehman and Moore. Perhaps the mechanical theory has the largest number of advocates, but recent studies seem to support the biochemical mode of action. Bergentz noted that platelet thrombi occur after injury and that fat emboli occur in conjunction with platelet emboli. As further evidence of this he noted a rise in red-cell mass triglycerides and a decrease in plasma triglycerides.

From the pathophysiologic standpoint, the lungs are the most common and important site of fat emboli. The chest roentgenogram frequently demonstrates diffuse fluffy infiltrates in both lung fields which may become manifest for the first time after an initial asymptomatic period of 24-72 hours. Arterial blood gases drawn at this time may show a decreased oxygen saturation associated with a decreased arterial carbon dioxide tension and a slightly elevated pH which is indicative of a mild diffusion block with hyperventilation in response to hypoxia. Compliance gradually decreases in those patients who exhibit progression of the pulmonary condition, and eventually in such cases cerebral and other organ involvement occurs. At autopsy the lungs are almost airless. There is marked capillary congestion and edema with areas of intra-alveolar hemorrhage and collapse alternating with zones of emphysema. Fat emboli ranging in size from 20-100 microns are found in arterioles and capillaries.

Treatment of fat embolism has been centered principally about efforts to combat respiratory failure. Heparin has been advocated; it is thought that by stimulating the release of lipoprotein lipase it might be of value in minimizing the initial embolization of fat. Its value may lie in its anti-inflammatory properties and ability to improve capillary blood flow. Low molecular weight dextran has been advocated as improving capillary blood flow by decreasing blood viscosity. Carbon dioxide inhalation has been used to increase cerebral blood flow, but high concentrations of oxygen and assisted respiration may afford greater benefit. Hypothermia may have some rationale by providing a decreased need for oxygen and its protective effect on the brain rather than any direct effect on respiratory failure.

The authors postulate that corticosteroids may be of value in the treatment of fat embolism by decreasing the permeability of cell membrane to toxic products, thereby inhibiting intracellular edema and cell destruction. Thus cortisone may inhibit the access of free fatty acids to the endothelial cell.

COMMENT: In both of the patients reported who were treated with cortisone, improvement was detected within a twelve-hour period. In one instance objective improvement was documented during that period by oxygen saturation studies. These responses are certainly impressive; but since the report deals with only two cases, these can serve only as preliminary, but nevertheless encouraging, observations. The patients reported seem to have been diagnosed as cases of fat embolism on clinical grounds. Although they exhibited rather classical clinical findings for such a diagnosis, it would have been of value to have obtained some substantiation from the laboratory standpoint.

Harold D. Kletschka, M.D.
Syracuse, New York

Ashbaugh, David G., and Petty, Thomas L.: Surg Gynec Obstet 123:493, 1966.

THE EARLY DIAGNOSIS OF BREAST CANCER

It has been strongly indicated but not completely demonstrated that early diagnosis will lower the over-all death rate from this disease, which has not changed much in thirty years. The concept that the smaller or earlier the lesion is when diagnosed, the better the chance for cure has not been disproven. All methods of detecting a nodule that may indicate the presence of cancer are reviewed in the order of their clinical significance.

Radioactive isotopes. To date, their use has been disappointing.

Sonarography (Ultra-Sound). Several ultrasonic scanning systems have been devised. Data has been hard to interpret. At present it is in the development stage.

The thermograph is a heat-sensing apparatus which records a heat photograph of thermal changes over an area of inflammation or a malignant lesion. There are several other physiologic as well as pathologic conditions that also become evident even in normal breasts and preg-

Continued

nancy. Thermography is unavailable and still in the research stage.

Transillumination may aid in differentiation of cysts and solid tumors; however, it will not determine benign from malignant tumors. Its function is limited but may suggest the use of a needle aspiration for diagnostic material.

Cytology. Cancer cells found in a discharge from the nipple makes a positive diagnosis; but a negative finding does not rule out cancer. The same conclusion holds true of fluid aspirated from a breast cyst. Needle biopsy of a breast tumor may reveal no cancer cells but does not contraindicate biopsy. The conventional block removal of the tumor with serial sections is the most accurate procedure. One or two sections through a small breast tumor may be inadequate and miss completely an area of cancer cells.

Breast self-examination. Records indicate that 90% of breast cancer is detected by the patients themselves. The American Cancer Society highly recommends self-examination and teaching women how to do one. A film teaching the technique has been made available by the Society, and they recommend this worth-while examination after each menstrual period.

Mammography. This has been demonstrated as a well established diagnostic tool in the detection of breast cancer. At present a study to determine the value of periodic screening and clinical examination in reducing breast cancer mortality is under way.

The success of mammography depends on the excellence of the films and the experience and training of the radiologist.

Indications for mammography are listed:

1. Any patient with a lump in one or both breasts;
2. A check on the opposite breast in a patient with carcinoma in one breast;
3. Any patient with a discharge from the nipple;
4. Patients with a strong family history of breast cancer;
5. Patients with known breast dysplasias;
6. Patients with large breasts. To this may be added a routine internal check of the remaining breast after one mastectomy.
7. A high index of suspicion. A careful examination is the most available and important factor in the detection of breast cancer symptomatic or asymptomatic.

Discussion. This article published in Ca, a Journal published by the American Cancer Society, is comprehensive and timely. It rates the experimental as well as the established means for detecting cancer of the breast.

The importance of multiple sections through a tumor should be stressed. I can recall one instance where the block was reported negative but the patient developed a local recurrence one year later. Re-examination of more sections of the original block revealed cancer cells, missed in the previous sections. Also, a second instance in which the 20th section revealed malignancy. There is no substitute for routine examinations for breast cancer.

Stanley R. Maxeiner, Sr., M.D.
Minneapolis, Minnesota

Botsford, Thomas W.: The Early Diagnosis of Breast Cancer. CA 16:4, 1966.

SIALOGRAPHY IN THE DIFFERENTIAL DIAGNOSIS OF PAROTID MASSES

The management of parotid tumors is hazardous and any diagnostic aid is welcome. Dr. Einstein presents his results from study of a consecutive series of 357 patients in whom he has used sialography as a diagnostic office procedure. Operation was performed on 265 patients; the remaining 92 patients were observed for a sufficient length of time to permit a satisfactory confirmation of the diagnosis.

Iodized oil in an amount of 0.5-1.5 cubic centimeters is injected through a blunt lacrimal duct needle using moderate pressure. Local anesthesia has been found to be unnecessary. Roentgenograms are then taken in stereoscopic posteroanterior and flat lateral views. The only untoward reaction noted has been a temporary swelling of the gland lasting a few hours.

The normal intact ductal system resembles a winter tree, with evenly distributed branches gently tapering off toward the periphery. Stensen's duct normally measures not more than 3 millimeters in diameter.

Pathologic findings can be classified as intrinsic space-occupying lesions, extrinsic indenting masses and abnormalities of the ductal system. Intrinsic space-occupying masses may produce rounded pressure defects in the major and lesser ducts. The ducts may be narrowed or stretched around the periphery of the mass, or the contrast material does not fill the branches in the area of the mass. Deep lobe masses show a rather characteristic medial ballooning, described as an umbrella effect. Extrinsic masses often cause indentation or rotation and displacement of the entire gland. Abnormalities of the ductal system are usually caused by inflammatory or neoplastic infiltrating processes. There may be variation in the caliber of the entire ductal system, with irregular interruption of the continuity of ducts, strictures, and sacculations.

The roentgenologic diagnosis proved correct in 96.6 per cent of the surgical patients studied.

COMMENT: It is apparent that this simple technique of sialography can contribute very useful and accurate information. Such a simple and safe procedure deserves wider application in the evaluation of lesions of the parotid gland.

Harold D. Kletschka, M.D.
Syracuse, New York

Einstein, Robert A. J.: Surg Gynec Obstet 122:1079, 1966

Emoluments

Your chief ambition will be to deserve the confidence of society: your greatest happiness to extend and strengthen that confidence . . . you will make science the groundwork of your reputation; and acts of intelligence, honor and benevolence the material of the superstructure. You will thus become shining lights of the profession: you will sit down with the great ones of the earth: the learned will thirst after your conversation; the rich will contribute their homage, the poor will call you blessed, and your names will live and be held in honour.

Dr. Daniel Drake
Address to the class of 1821
of the Medical College of Ohio

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Rees B. Rees, M.D., San Francisco, Calif.—*Dermatology*
Jose M. de la Vega, M.D., Mexico, D. F.—*Gastroenterology*
Nicholas J. Pisacano, M.D., Lexington, Ky.—*General Practice*
Gordon W. Douglas, M.D., New York, N. Y.—*Gynecology*
Robert C. Hartmann, M.D., Nashville, Tenn.—*Internal Medicine*
C. Thorpe Ray, M.D., Columbia, Mo.—*Internal Medicine*
A. Earl Walker, M.D., Baltimore, Md.—*Neurological Surgery*
Humbert L. Riva, M.D., East Orange, N. J.—*Obstetrics*
Arthur H. Keeney, M.D., Philadelphia, Pa.—*Ophthalmology*
Robert W. Bailey, M.D., Ann Arbor, Mich.—*Orthopedic Surgery*
John J. Conley, M.D., New York, N. Y.—*Otorhinolaryngology*
F. William Sunderman, M.D., Philadelphia, Pa.—*Pathology*
Alexander J. Schaffer, M.D., Baltimore, Md.—*Pediatrics*
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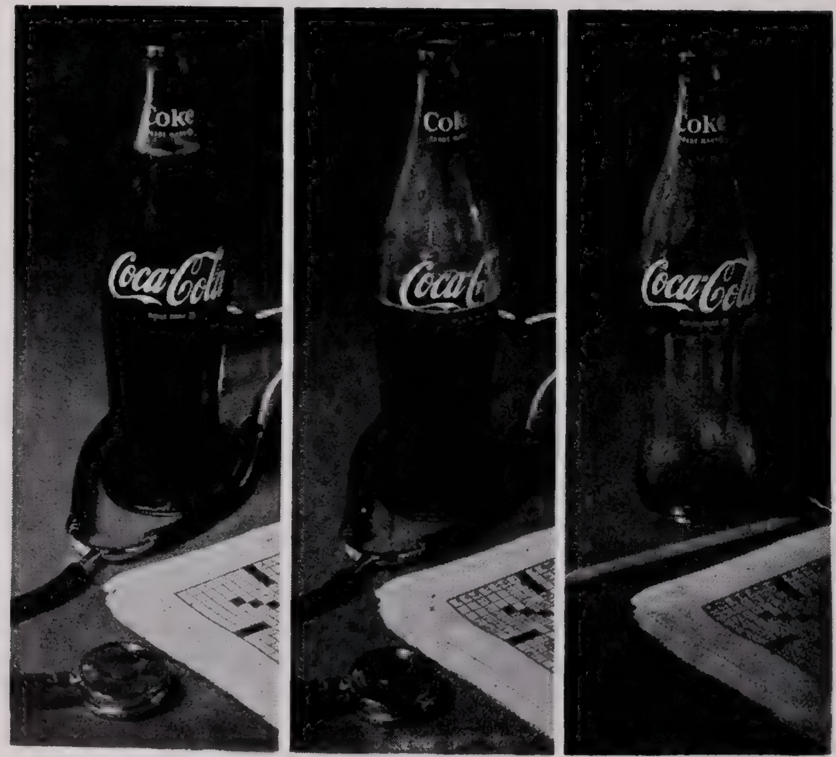

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Book Reviews

Education does not mean teaching people to know what they do not know; it means teaching them to behave as they do not behave. — Ruskin.

A CURRENT PEDIATRIC THERAPY — 1966-1967 — Edited by Sydney S. Gellis, M.D., and Benjamin Kagan, M.D. W. B. Saunders and Co., Philadelphia and London. January 11, 1966. Price $17.50. and

PEDIATRIC THERAPY — Edited by Harry C. Shirkey, C. V. Mosby Co., St. Louis, Missouri, 1966. $18.50.

These second editions of the two major hard-cover volumes on Pediatric Therapy attempt to provide a comprehensive account of therapies for diseases of infancy and childhood. Both books are well written and appear to succeed in their attempt. No single reviewer could attempt to question the quality and authority of the many experts who have contributed details of treatment of one or more of the diseases of children. Both books provide competent guidance to any physician who wants an expert's consultation on therapy for a problem on which he does not have current information.

The justification for a text of this type is that new drugs, antimicrobial agents, vaccines, etc. appear each year, with reports of their value so widely scattered through the literature that no individual physician is likely to be aware of them. Yet every doctor wants and welcomes medical guidance beyond the reports available from the pharmaceutical industry. In so far as Gellis' and Kagan's book is directed to this end, its purpose is obviously valid and desirable.

Since the second editions of CURRENT PEDIATRIC THERAPY and PEDIATRIC THERAPY have followed so close upon the first editions, it would appear that text books of this type are highly popular because of their currency and comprehensiveness, making available to the practitioner many details of treatment otherwise scattered throughout the literature. The validity of these approaches on a long-term basis is something that each individual must ascertain for himself. If he thinks that a text book of this type will be valuable to him, that is sufficient indication for purchase of either book. If he wishes an additional consultation on therapy, he might purchase both. CURRENT PEDIATRIC THERAPY has the edge in comprehensiveness, PEDIATRIC THERAPY in detail.

Warren J. Warwick, M.D.
Minneapolis, Minnesota

ENCYCLOPEDIA FOR MEDICAL ASSISTANTS — Louis Brachman, M.D., Cathedral Square, 448 pages, $14.95.

This book is as fascinating as it is instructive. It has some interesting facets for the physician as well as for his medical assistants. "Witch doctors dispense all medicines in powder form — and so they snip off a piece of dried-up snakeskin and grind it in a mortar with a stone pestle, adding a little powdered dragon's blood and the bitter-tasting root of a plant which produces great white blossoms when the moon is full, and finally some pulverized rhinoceros hide. The dark brown powder which results must be sniffed like snuff in order to drive away the evil spirits".

The book is well bound and the type is large enough for easy reading. The dictionary of medical terms and the index are adequate.

Carl O. Rice, M.D.
Minneapolis, Minnesota

SYMPOSIUM ON SURGERY OF THE OCULAR ADNEXA — New Orleans Academy of Ophthalmology, St. Louis. C. V. Mosby Company, 1966, 230 pages, Black and white illustrations, Chapter references, index, Price $16.00.

This book contains the presentations and "round table" discussion from the fourteenth annual meeting of the New Orleans Academy of Ophthalmology held in February 1965. As usual, the most noted contributors to the field of ophthalmic plastic and adnexal (excluding the eyeball itself) surgery were on hand. Their collected topics cover a good deal of the subject, forming a valuable reference and study volume for the ophthalmologist. Among the topics covered are: basic principles of plastic surgery; reconstructive surgery for burns of the lids; correction of ptosis (drooping lid); tumors of the lacrimal gland; surgery of the lacrimal drainage system; tumors of the lid, conjunctiva and orbit; and correction of entropian and ectropion (in and out turning respectively of the lid).

William S. McClanahan, M.D.
Meriden, Connecticut

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Special Article

The Masonic Medical Research Laboratory

GORDON K. MOE, M.D., Ph.D.
Utica, New York

LOCATED ON the campus of the Masonic Home in Utica, New York, is a unique research institute, supported by the Masonic Fraternity of New York State and loosely affiliated with the State University's Upstate Medical Center in Syracuse and with other institutions of higher learning in the area. The Laboratory is the operating agency of the Masonic Foundation for Medical Research and Human Welfare, which was chartered as a non-profit corporation in 1947. The Foundation is governed by a board of nine distinguished business and professional leaders, prominent in civic, humanitarian, and Masonic affairs, under the leadership of President David R. Cunnison, of Bellerose, Long Island. After a period of seven years during which the Foundation granted close to $2,000,000 in support of research in rheumatic fever and related diseases, the Board of Directors elected to build, equip, and operate its own research facility. With the advice of a distinguished panel of medical advisors, including the original Director of Research, Dr. J. Murray Steele, a modern research laboratory was completed in the spring of 1958.

In 1957, Dr. Norman S. Olsen was appointed Assistant Director and given the responsibility for furnishing, equipping, and staffing the new laboratory and initiating its first research program in experimental atherosclerosis. Dr. Olsen received his Ph.D. in biochemistry from the University of Minnesota in 1942. In 1959, following the resignation of Dr. Steele, the author accepted appointment as Director of Research, sharing responsibility with Dr. Olsen and with Dr. Verner J. Wulff, formerly chairman of the Department of Zoology at Syracuse University. Within a few weeks after full-scale operation of the Laboratory began in 1960, Dr. Olsen and his family died in a fire at their home. Despite this tragic beginning, the Laboratory has steadily

Continued

grown to its present complement of twelve full-time professional scientists and 25 assistants.

Professional Staff

Gordon K. Moe, Ph.D. (Minnesota), M.D. (Harvard). Director of Research.

Verner J. Wulff, Ph.D. (Iowa). Associate Director of Research.

Mildred Behrens, Ph.D. (Syracuse). Research Scientist.

Lawrence Cerny, Ph.D. (Ghent). Established Investigator, American Heart Association.

Roderick Childers, M.D. (Dublin). Visiting Scientist, 1966.

Joseph Falzone, M.D., Ph.D. (Washington University). Senior Research Scientist.

Jaok Han, M.D. (Taegu), Ph.D. (S.U.N.Y.). Research Scientist.

Carlos Mendez, M.D. (Mexico). Senior Research Scientist.

John Merideth, M.D. (Kansas). U.S.P.H.S. Postdoctoral Fellow.

Harvey Samis, Ph.D. (Brown). Research Scientist.

William Stoller, Ph.D. (Syracuse). U.S.P.H.S. Postdoctoral Fellow.

Richard Tuttle, Ph.D. (S.U.N.Y.). Research Scientist.

Support of the Laboratory

Although the Laboratory has been assisted by grants from the National Institutes of Health, The American Heart Association and its Onondaga and Oneida County Chapters, the Life Insurance Medical Research Fund, the Atomic Energy Commission, the Upjohn Company, the Olsen Memorial Fund (to which many Minnesota friends have contributed) and various private donors, still the major support of our activities, more than 70%, comes from the voluntary contributions of the Masons of New York State through their annual Brotherhood Fund Campaign.

Academic Affiliations

The Laboratory maintains a loose but functionally effective relationship with Syracuse University, State University of New York Medical Center in Syracuse, and local colleges. Four graduate degrees have been granted by the Syracuse institutions on the basis of work conducted at the Laboratory, and members of the scientific staff hold academic appointments at Syracuse University, at the Medical College, and at Utica College of Syracuse University. Numerous research projects have been conducted in collaboration with investigators at these institutions.

The Research Program

The original and current research emphasis of the Laboratory is gerontology, defined in the broad sense as anything which happens after conception. Within this wide domain, some five major research programs are in progress at the present time.

1. *Nucleic acid metabolism as a function of age.* This program, under the direction of Dr. Wulff, has generated one of the most provocative hypotheses in the area of experimental gerontology. In 1961 it was observed that the metabolic turnover of ribonucleic acid (RNA) was significantly greater in the tissues of old rats than in young adults.[1-4] This surprising observation led to the postulate that aging and ultimate death of cells result from the gradual accumulation of errors in the nuclear DNA templates responsible for the synthesis of messenger RNA. Such errors (which might be designated "somatic mutations") could conceivably be cross-linkages between bases in twin strands of DNA, induced, for example, by ionizing radiation; but however they come about, the end result would be the synthesis of faulty or totally inappropriate messenger RNA. This deficiency would be reflected in a comparable deficiency of the enzyme molecules whose synthesis is directed by messenger RNA. So long as functional sites for the nuclear synthesis of RNA exist, the deficiency can be at least partially compensated by an increase in the rate of synthesis (i.e., an increased rate of turnover of RNA) ; but when adequate supplies of effective messenger RNA can no longer be produced, the cell must die.

The "error hypothesis" has survived many crucial tests but cannot be considered as proved. Assuming that errors do occur, and that they occur randomly, it is obvious that one cell may become deficient in enzyme "X", while its neighbor is inadequately supplied with enzyme "Y". In the tissue as a whole, no *single* enzyme may be lacking, but an individual cell may fail to survive the accumulated damage to its own synthetic machinery.

These investigations, which describe a major biochemical difference between the tissues of young and old animals, engage the full time attention of Drs. Samis, Falzone, and Stoller in addition to Dr. Wulff.

2. *Vasomotor regulation.* In 1960 Dr. Tuttle began a series of studies to define the integration of hemodynamic reflexes at the medullary and spinal cord level in the cat. In the course of these investigations he discovered a medullary site at which a brief period of moderate stimulation induced a delayed but profound hypotensive response, often leading to irreversible circulatory failure.[5] We are accustomed to look upon blood pressure regulation as the integration of cholinergic and adrenergic effector mechanisms, but neither activation of cholinergic, nor suppression of adrenergic systems should be expected to lead to a lethal outcome. Further study demonstrated that histamine liberation was also involved in the expression of the hypotensive response.[6] This observation led in turn to an investigation of the possible role of histamine in the operation of less drastic vasomotor regulations. It now appears certain that histamine is liberated at sites which directly affect vascular resistance in response to such physiologically benign stimuli as elevation of carotid sinus pressure. Histamine, so often invoked to explain pathological phenomena, now emerges as one of a family of functional mediators of normal vasomotor regulation.

3. *Rheology of blood.* Because of its non-Newtonian properties, blood has long distressed biophysicists. Its behavior in small tubes departs from the simple viscosity characteristics defined long ago by Poiseuille. When one wishes to describe in an all-inclusive equation the relation between pressure and flow of blood in tubes rigid or elastic, cylindrical or tapered, large or small, and at rates steady or pulsatile, the complications compound themselves. Yet this is the objective of Dr. Cerny. Dr. Cerný, who spent a fellowship year at the University of Minnesota with the late Dr. Cyrus Barnum

The Masonic Medical Research Laboratory at the time of its completion in 1958.

Continued

in 1958-59, has come close to defining a general flow equation for blood, and also for some of the macromolecular substances proposed as plasma substitutes.[7]

The importance of Dr. Cerny's studies becomes obvious when one considers the characteristics of the "ideal" plasma substitute. It must of course be non-toxic. It should develop an oncotic pressure comparable to that of normal plasma proteins and be retained within the blood stream; it should not be rapidly metabolized or excreted; nor should it be too viscous at effective concentrations in blood. Clearly, it is important to understand the viscous properties of such a substance, especially when mixed with blood, and particularly when flowing in tubes of capillary size. A substance with the characteristics of a fluid in the aorta and those of a gel in the capillaries could hardly serve a useful function.

4. *Cardiac impulse generation and transmission.* An understanding of the genesis and maintenance of cardiac arrhythmias should provide the necessary background for specific prophylaxis and therapy. One of the major efforts of the Laboratory has been the development and analysis of experimental models of clinically important arrhythmias: atrial flutter and fibrillation; idioventricular rhythms; ventricular fibrillation; A-V nodal reciprocal rhythms; functional heart block; "concealed" A-V conduction.

Dr. Mendez has succeeded in demonstrating, in *in-vitro* preparations of the rabbit A-V nodal region, the functional and morphologic basis of A-V reciprocation (atrial and ventricular "echoes"; A-V nodal tachycardia). Two propagation pathways were found within the atrial margin of the node. The refractory periods of these pathways differ enough to permit an impulse to enter one route at a time when the other is still incapable of impulse transmission, whereupon a return route for an echo becomes available. Repetition of the event can, under appropriate circumstances, lead to a self-sustained circus movement tachycardia.[8]

In a comprehensive study of the role of inhomogeneity in the genesis of self-sustained cardiac rhythms, it has been suggested that dispersion of the recovery times of neighboring elements may provide the adequate substrate for reentrant activity. The postulate was shown to be a feasible mechanism for atrial fibrillation in a computer model,[9] and Dr. Han has shown that agencies which increase dispersion also favor the development of spontaneous rhythms.[10] Recent observations in experimental animals, conducted by Dr. Han, provide an explanation for the greater incidence of ectopic ventricular activity at slow heart rates.

Collaborating in these studies at the present time are Dr. Childers, on leave from the University of Chicago, and Dr. Merideth, on leave from the Mayo Clinic as a candidate for the Ph.D. degree in the Mayo Graduate School of Medicine.

5. *Photoreception in the horseshoe crab.* Many visual physiologists make use of this ancient creature because of the simplicity of the photoreceptive units in its multi-faceted lateral eye. Dr. Behrens set out to demonstrate which of the cell types in the visual unit served as sense receptors and which as neural elements, and how the photic stimulus is transduced to nerve impulses. By means of intracellular microelectrodes, she has recorded the response to light of one of the receptor cells (the retinula cells) simultaneously with the response of the neural element (eccentric cell) of the same facet. Beyond that, she has also managed to stain each of the cells by the electrophoretic injection of different dyes, so that electrical responses could be clearly identified with cell types.[11] Recently, she has recorded the effects of destruction of single sense cells on the behavior of the visual receptor.

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3. Wulff, V. J., Quastler, H., and Sherman, F. G.: The Incorporation of H^3-Cytidine into some Viscera and Skeletal Muscle of Young and Old Mice. J Geront 19:294, 1964.

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History of Medicine

A Brief History of the State University of New York Upstate Medical Center

MEDICAL EDUCATION in the United States goes back only for the short period of 200 years to the founding of the first school at the University of Pennsylvania in 1764. In the ensuing 100 years medical education passed through many phases and weathered many such storms as quack theories of practice; dissension among faculties as to what should be taught and how; who was authorized to grant degrees; and where did one obtain the bodies needed for dissection.

Medical education in New York State began in 1767 with the establishment of the Medical Faculty of King's College (later Columbia). The faculty of this school was distinguished and consisted of strong-minded individuals who did not always see eye to eye. In 1826 the faculty split, and the dissident group, led by David Hosack, formed the Rutger's College Medical Department, located in New York City. Since Rutgers was a New Jersey institution (formerly called Queen's College as the counterpart to Columbia), it was confronted with a legal action which held that New York State's rights were infringed under this arrangement. It was therefore necessary to find a New York school which could grant the necessary degree, and Geneva College (later Hobart and William Smith Colleges), which had the power to confer collegiate degrees and diplomas of any sort whatever, was willing to do this. One suspects, however, that part of its motivation was a desire to compete with its rival upstate institution, the College of Physicians and Surgeons of the Western District at Fairfield.

The new arrangement continued but a short time, for the College of Physicians and Surgeons at Columbia, fearing that a new school would mean the demise of the older, took the case to the State Supreme Court which declared the absentee granting of degrees illegal. The Rutgers Medical Faculty thus ceased to exist after four years of operation, during which time it had produced 104 graduates.

Geneva College then organized its own medical institution (Figure 3) which was founded in 1834 and began classes in 1835. The Geneva Medical institution prospered for some time; indeed, its success caused the school at Fairfield to close its doors in 1840. At that time three members of the Fairfield faculty joined Geneva, while others went on to the newly formed Albany Medical College.

In the late 1840s the Geneva Medical College received an application which was to precipitate on the school both fame and opprobrium. Elizabeth Blackwell (Figures 1 and 2) had applied to, and been rejected by, 13 of the country's 36 medical schools when she turned to Geneva. The faculty was either unable or unwilling to reach a decision on the matter and it was referred to the student body. The students, not entirely sure that the application was not a jest being perpetrated on them by a rival school, unanimously voted their approval. Miss Blackwell received a copy of their resolution and wrote that "the following unique and manly letter, . . . I had afterwards copied on parchment and esteem one of my most valued possessions."

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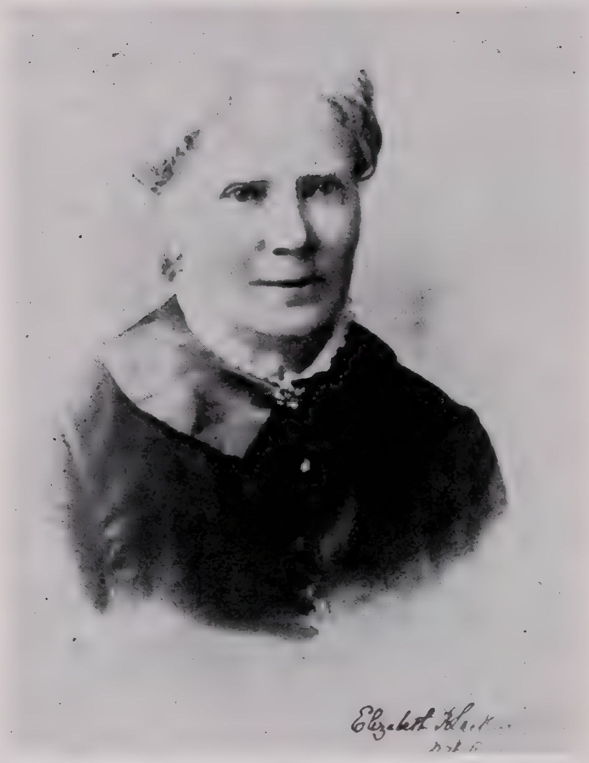


Fig. 1 — Photograph of Dr. Elizabeth Blackwell. She was the first woman to receive the M.D. degree from an American medical school.

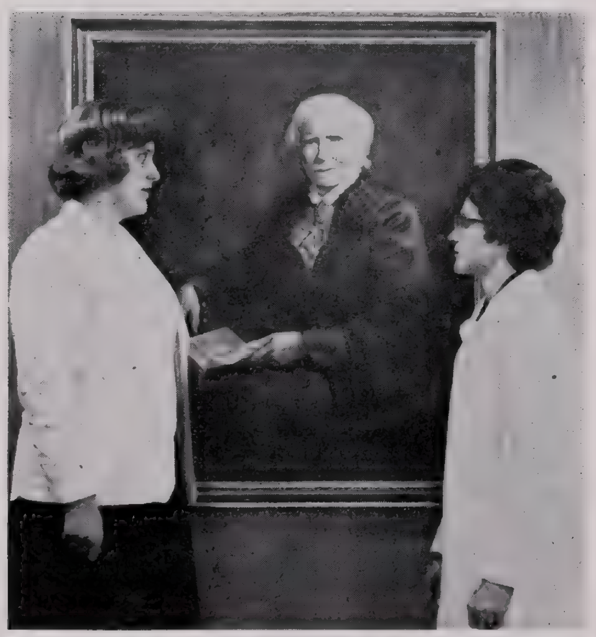


Fig. 2 — Portrait of Dr. Elizabeth Blackwell presented to the Upstate Medical Center in 1964 by the Women's Medical Sorority of the Upstate Medical Center. Dedication was made to perpetuate the memory of Dr. Blackwell. Dr. Patricia Numann (left), President of the Women's Medical Sorority and Dr. Mary Voorhess made the presentation.

At a meeting of the entire medical class of Geneva Medical College, held this day, October 20, 1847, the following resolutions were unanimously adopted:

> 1. Resolved — That one of the radical principles of a Republican Government is the universal education of both sexes; that to every branch of scientific education the door should be open equally to all; that the application of Elizabeth Blackwell to become a member of our class meets our entire approbation; and in extending our unanimous invitation we pledge ourselves that no conduct of ours shall cause her to regret her attendance at this institution.
>
> 2. Resolved — That a copy of these proceedings be signed by the chairman and transmitted to Elizabeth Blackwell.
>
> T. J. Stratton, Chairman.

Accordingly, she departed from Philadelphia on November 4, and, after a two-day journey reached Geneva at 11:00 p.m. on November 6, 1847.

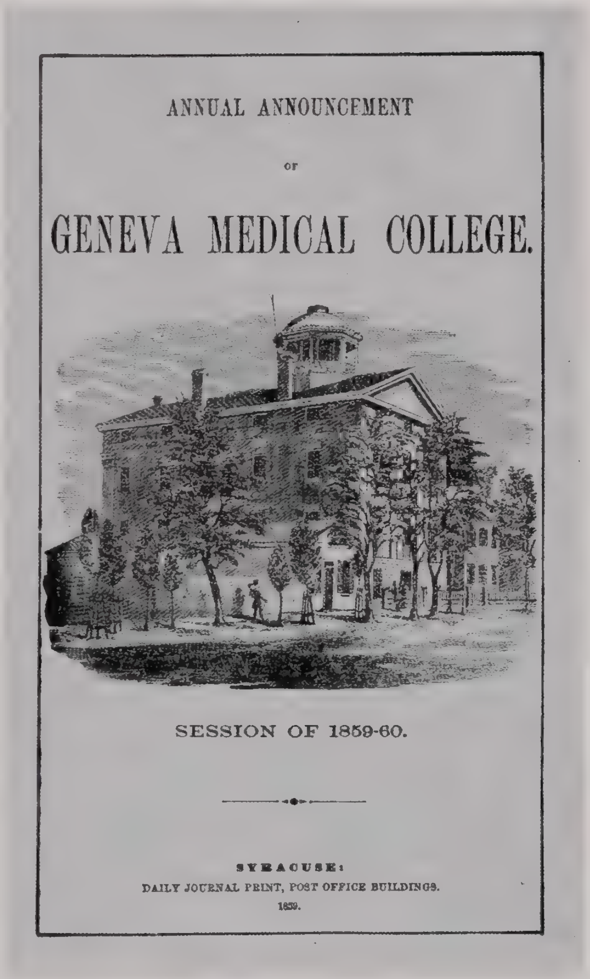
Thus it was that Geneva earned the distinction of being the first school in the United States to award the M.D. degree to a woman. After completing the required course of two sets of identical lectures, the normal mode of medical education of the day, Elizabeth Blackwell was graduated.

The public commencement of Elizabeth Blackwell's class took place on January 23, 1849. The valedictory address was given by Dr. Charles Alfred Lee, Professor of General Pathology and Materia Medica, and consisted in the main of a recapitulation of the ethics of the profession. Perhaps more unusual is the section which he devotes to a discussion of medical charlatans. Explaining that society consists of three classes, the medical skeptic, the overly credulous and superstitious, and those who view medicine "as one of the main pillars on which the welfare and happiness of society rests," he enumerates the current fads and theories and urges the student not to lose his interest in medical education. He is overly optimistic when he states that future humbugs will have but a sandy foundation due to the fact that "public credulity has been stretched until it has nearly snapped in twain," for the quack is not yet vanquished and a great deal more sophisticated.

In regard to the singular fact that a woman was being graduated for the first time he made the following comments:

"An event connected with the proceedings of this day deserves some notice on this occasion, calculated as it is to excite curiosity and comment, and to be held up as an example for other institutions to imitate or condemn. I mean the conferring of the degree of M.D. upon one of that sex which is generally supposed to be wanting in the physical, if not moral, qualifications necessary for the successful practice of the Healing Art. So far as I am informed, this is the first instance, in this country, or any other, where a female has graduated in medicine after having gone through the regular prescribed course and term of study; and in the present instance it is my duty to add, without the omission or the slighting of any branch of study, and that too in so thorough a manner as to leave nothing unattempted or unattained which it is necessary for one to know who expects to practice with honor and success in every department of the profession.

"Such an instance of self-sacrificing devotion to science; of perseverance under difficulties, and obstacles next to insurmountable — of unremitting, unrelaxing toil, in pursuit of that knowledge, so important to, and yet so rarely possessed by her sex — and all this for the purpose of mitigating human misery, relieving the sick, and extending her sphere of usefulness in the world — this, I say, deserves, as it will receive, the heartfelt approbation of every generous and humane mind. This event will stand forth hereafter as a memorable example of what woman can undertake and accomplish, too, when stimulated by the love of science and a noble spirit of philanthropy. Why should medical science be monopolized by us alone? Why should woman be prohibited from fulfilling her mission as a ministering angel to the sick, furnished not only with the softer and kindlier attributes of her sex, but with all the appliances and resources of science? If she feels called to this life of toil and responsibility, and gives evidence of her qualifications for such a calling, in humanity's name, let her take her rank among the disciples of Aesculapius and be



ANNUAL ANNOUNCEMENT

OF

GENEVA MEDICAL COLLEGE.

SESSION OF 1859-60.

SYRACUSE:
DAILY JOURNAL PRINT, POST OFFICE BUILDINGS.
1859.

Fig. 3 — Announcement of Geneva Medical College appearing in 1859.

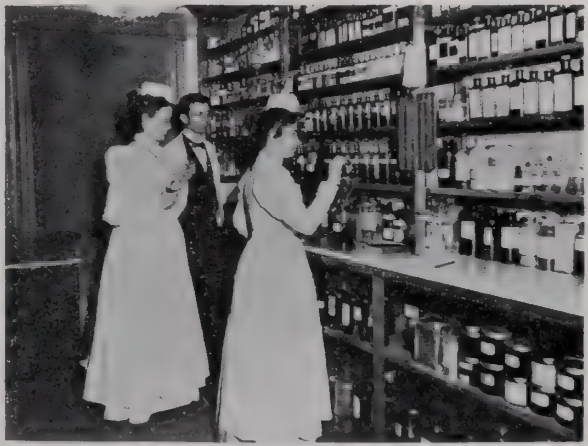


Fig. 4 — Syracuse Free Dispensary, 1899.

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honored for her self-sacrificing choice. Such cases must ever be too few to disturb the existing relations of society, or excite any other feeling on our part than admiration at the heroism displayed and sympathy for the sufferings voluntarily assumed! God speed her, then, in her errand of mercy and crown her efforts with abundant success!"

The event was so notable that even *Punch* could not refrain from pointing out the moral lesson to its readers and published the following note and verse:

AN M.D. IN A GOWN

The MEDICAL TIMES *of the 21st ult. contains a full, true, and particular account of the admission of a young lady, Miss Elizabeth Blackwell, by the General [Geneva] Medical College, in the State of New York, to a physician's degree. Miss Blackwell had duly attended Lectures at the College, and received a formal diploma, under the title of "Domina," which was the only feminine that the Senate could find for Doctor.* PUNCH *really thinks this is a case for a copy of verses, which he accordingly subjoins, in honour of the fair M.D.*

Not always is the warrior male,
  Nor masculine the sailor;
We all know ZARAGOSSA'S tale,
  We've all heard "Billy Taylor."
But far a nobler heroine, she
  Who won the palm of knowledge,
And took a Medical Degree,
  By study at her College.

They talk about the gentler sex
  Mankind in sickness tending,
And o'er the patient's couch their necks
  Solicitously bending;
But what avails solicitude
  In fever or in phthisic
If lovely woman's not imbued
  With one idea of physic?

Young ladies all, of every clime,
  Especially of Britain,
Who wholly occupy your time
  In novels or in knitting,
Whose highest skill is but to play,
  Sing, dance, or French to clack well,
Reflect on the example, pray,
  Of excellent MISS BLACKWELL!

Think, if you had a brother ill,
  A husband, or a lover,
And could prescribe the draught or pill
  Whereby he might recover;
How much more useful this would be,
  Oh, sister, wife, or daughter!
Than merely handing him beef-tea,
  Gruel, or toast-and-water.

Ye bachelors about to wed
  In youth's unthinking hey-day,
Who look upon a furnish'd head
  As horrid for a lady,
Who'd call a female doctor "blue";
  You'd spare your sneers, I rather
Think, my young fellows, if you knew
  What physic costs a father!

How much more blest were married life
  To men of small condition,
If every one could have his wife
  For family physician;
His nursery kept from ailments free,
  By proper regulation,
And for advice his only fee
  A thankful salutation.

For DOCTRIX BLACKWELL — that's the way
  To dub in rightful gender —
In her profession, ever may
  Prosperity attend her!
"Punch" a gold-handled parasol
  Suggests for presentation
To one so well deserving all
  Esteem and admiration.*

The faculty was perhaps a little surprised at its liberality, nonetheless, for two years

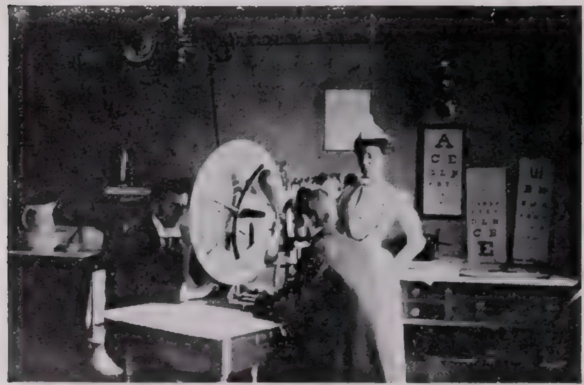

Fig. 5 — Eye room, Syracuse Free Dispensary, 1897-1904.

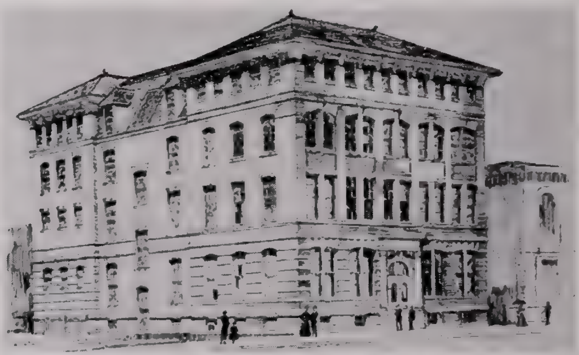

Fig. 6 — Syracuse University Medical College Building, opened in 1896.

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*Punch 16:226, 1849.

later, when Elizabeth's sister Emily applied for admission, she was denied, and after much difficulty was finally admitted to Western Reserve.

Elizabeth Blackwell went on to become a most distinguished alumna of the school. In 1857, together with her sister, she established the New York Infirmary, the first such institution of its kind devoted to women. Later she was instrumental in forming the Nursing Corps for the Union Army during the Civil War (she was not accepted as an equal by the Army physicians).

She ended her life in England still fighting for the rights of women and numbered among her friends the redoubtable Florence Nightingale. Her long and useful career ended in 1910 at the age of 89.

The College reached its zenith in the 1840s. In 1843, 195 students were enrolled, the largest number recorded, and in 1846, 49 candidates received degrees. The number of students began to decline in the 1850s, and in 1854 there were no graduates because the course of lectures was interrupted. The Civil War years did not appreciably affect the number of students, but there was a brief resurgence in the number of graduates in 1866, 1867, and 1868.

The decline was partly due to the establishment of the medical department of the University of Buffalo, which drew students and faculty away from Geneva. The difficulties presented by the smallness of the town caused the faculty to investigate an alliance with the newly organized university at Syracuse, which also had the advantage of providing two new hospitals there for clinical work.

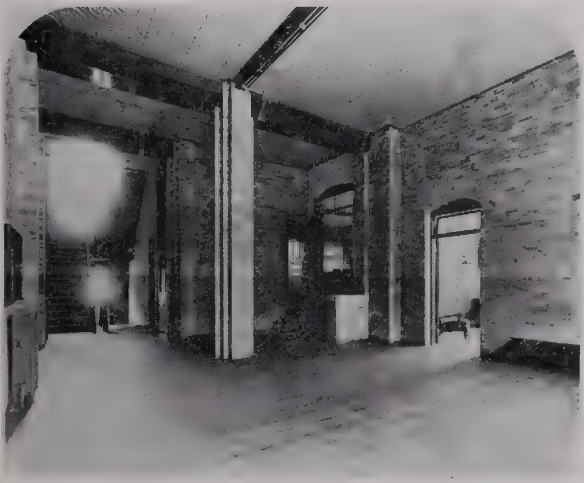

Fig. 7 — First floor of Syracuse University Medical College, 1896.

Bringing the library and anatomical museum with them, members of the faculty moved to Syracuse in 1872 and began the first session as the medical department of Syracuse University in October of that year. All told, some 849 doctors had been graduated from the Geneva campus.

The Medical Department of Syracuse University pioneered in many reforms in medical education and as early as 1875 had adopted the three-year graded course system following the lead of the Chicago Medical College which had begun the program in 1859 and Harvard which started it in 1871. The medical school was the first in the country to install and equip a physiological laboratory (Figure 8) for students, an innovation begun when it opened a new building (Figures 6 and 7) in 1896. An interesting feature was the pulley system, connected to a central power source, used to drive all kymographs at a standard speed.

The State University of New York was organized in 1948. It first purchased the Long Island College of Medicine in Brooklyn, which became the Downstate Medical Center, and then in 1950 purchased the

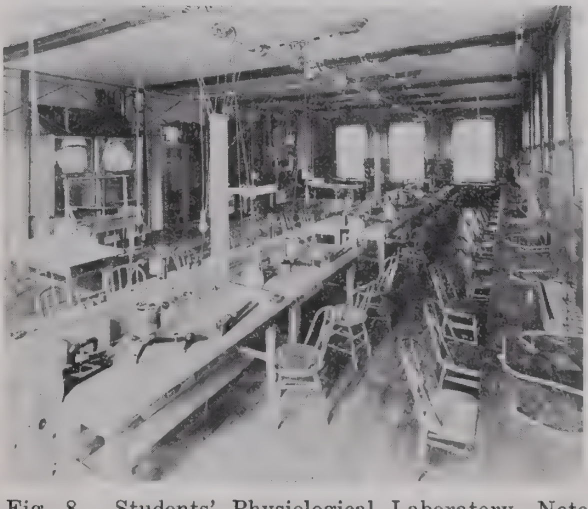

Fig. 8 — Students' Physiological Laboratory. Note unique pulley system, connected to a central power source, used to standardize speed of all the kymographs.

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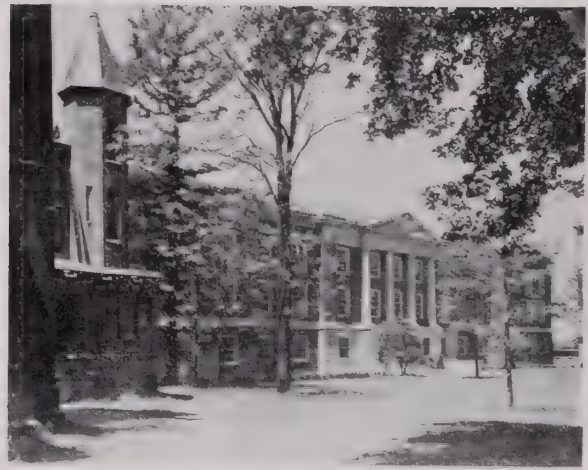

Fig. 9 — Syracuse University Medical School, 1937-1958. Yates Castle is on the left.

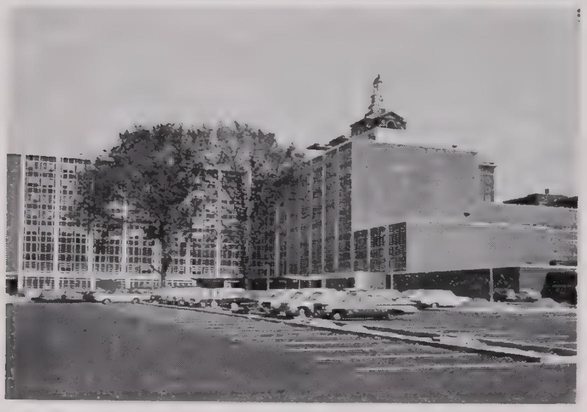

Fig. 10 — New State University Hospital, opened for service in July, 1965.

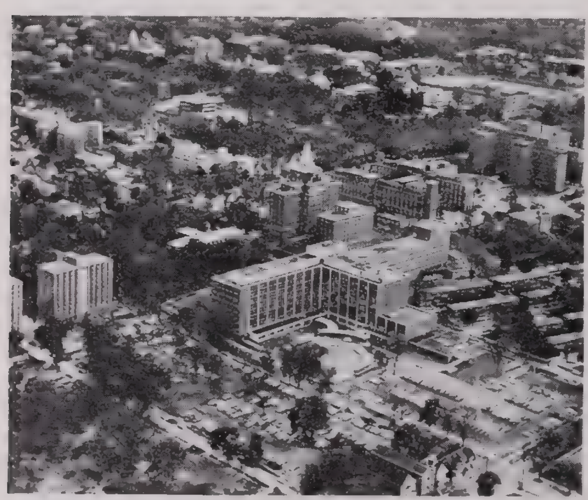

Fig. 11 — Present Upstate Medical Center Complex. The new State University Hospital is in the foreground. The U. S. Veterans Administration Hospital is to the far right of the picture. The building with the tower is Memorial Hospital with the administration and basic science building to its right and Crouse-Irving Hospital behind.

College of Medicine (Figure 9) and the School of Public Health Nursing from Syracuse University, as the nucleus of the Upstate Medical Center. It is ironic that the third State University Medical Center should be the school at Buffalo which was so influential in the decline of the Geneva Medical College. Buffalo joined the State system in 1960.

The medical school at the Upstate Medical Center was reorganized during the 1950s, the curriculum enlarged and a new wing added to the Basic Science Building, three floors of which now house the medical library, with its original collection from the Geneva Medical College.

In 1961 ground was broken for the new Hospital (Figure 10), within a few hundred feet of the Basic Science Building. The Hospital's three wings house expanded research facilities, a 375-bed hospital, and the outpatient services of the Center, and were opened for service in July 1965.

Twin residences, situated on Elizabeth Blackwell Street to the north of the Hospital, house some 540 of the Medical Center's students and staff.

The next construction phase consisting of a student activities building which will be located between the two residence units is now in progress. Also included in the current expansion is the construction of a computing facility which will bring together and house four major activities: the State University of New York Computerized Biomedical Information Network, the research data processing center for the entire Medical Center, the administrative data processing facility, and the patient data storage and retrieval center. Completion of this program is expected in 1968.

The Hospital of the Good Shepherd

The new State University Hospital is the successor of the House of the Good Shepherd which was founded in 1872 as the teaching unit of the new College of Medicine. Housed in frame buildings until 1901, it was replaced by the still existing structure, then one of the most modern hospitals in the country. It featured self-service automatic elevators, centralized ventilation systems which allowed the air to be changed in each ward every eight minutes, and was completely wired for electricity and telephone.

In the early 1880s women took their place as nurses in the Hospital. They were untrained and received what instruction they could from the physicians and from each other. In 1885 the Hospital established a school for nurses' training and accepted a class of six for a two-year course. The first group graduated in 1887, as did a class at Johns Hopkins Hospital, the first such schools in the country to offer nursing education.

The Hospital of the Good Shepherd did not officially become a part of the Syracuse University until 1915, when the shift to University auspices was necesitated by the need for financial support and assistance. At that time its School of Nursing was also incorporated into the University structure where it remains one of the professional schools, giving both B.S. and M.S. degrees. The Upstate Medical Center Library provides the instructional resources for this program's clinical portions, and practical training is undertaken in the new Hospital.

The Syracuse Free Dispensary

Originally founded in 1888 by a group of local businessmen and physicians under the leadership of Dr. John Van Duyn, the Dispensary (Figures 4 and 5) continued the work begun by Dr. Van Duyn and other private physicians. In the first 30 years it treated some 51,000 patients at a cost to each of approximately ten cents per prescription. By 1966 the Dispensary was treating some 80,000 patients a year.

There have been four homes for the institution prior to its move into the State University Hospital, each reflecting the increasing importance of the institution to the community. In 1917 the Dispensary began its formal association with the College of Medicine in new quarters built by the University, and since 1950 it has served as the Upstate Medical Center's outpatient department.

The objectives of the Dispensary were stated in the articles of incorporation on July 17, 1888, and were "the providing and furnishing medical and surgical aid to such persons as may be in need thereof and unable by reason of poverty to procure the same: the more successful treatment and control of disease and the advancement of medical science."

The hopes of Dr. Herman G. Weiskotten, Dean of the School from 1922 to 1951, that the Dispensary would some day be housed in a wing of the Medical School have been realized and, as Dr. Alphonse M. Schwitalla said at the 50th Anniversary ceremonies in 1938, this arrangement will "lay the foundation for a greater and more efficient and better out-patient department."

"Let Each Become All He is Capable of Being"

The educational program has grown to include the College of Medicine, a two-year School of Nursing granting an Associate in Applied Science degree (since 1959), graduate programs in the medical sciences leading to M.S. or Ph.D. degrees, and extensive Intern-Resident programs. The Medical Center's College of Allied Health Professions opened in the fall of 1965 with the first class of the School of X-ray Technology, a two-year program leading to an Associate in Applied Science degree, and the first class in the Medical Technology program. Students enter this program after completing two years of college, and after two years at the Medical Center receive a B.S. degree. In 1967 a Nursing program leading to a B.S. degree is planned. Other schools in the supportive medical sciences are also planned.

The Medical Center (Figure 11) is a complex of affiliated hospitals which can accommodate over 1800 patients. Currently, affiliations are maintained with City Hospital; Syracuse Memorial Hospital; Community-General Hospital; St. Mary's Hospital; City Health Department Bureau of Maternal and Child Care; Crouse-Irving Hospital; Syracuse Psychiatric Hospital; the U. S. Veterans Administration; St. Joseph's Hospital; and the State University Hospital. Within the next ten years the size of the Medical

Continued

Center complex will expand to accommodate more than 3,000 patients, as a new short-term mental hospital, additional floors for the State University Hospital, and a new and expanded Crouse-Irving Hospital are constructed.

Irwin H. Pizer, M.S.*
Syracuse, New York

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*Director of the Library and Associate Professor of Medical History, State University of New York, Upstate Medical Center.

Green Medicinals

Herbs for the Lungs

Ecclesiasticus said: The Lord hath created medicines out of the earth and a wise man will not abhor them. Among the herbal remedies for lungs are angelica, borage, forget-me-not, hyssop, mullein, primrose, sundew, vipers bugloss, and wild cherry.

For a tonic using borage one can drink:

Borage in a Cool Tankard

A quart of mild ale, a glass of white wine, one of brandy, one of capillaire, the juice of a lemon, the peel pared thin, nutmeg grated on top, a sprig of borage, a bit of toasted bread and a few of the blue flowers floating on top. — Dr. Kitchener (1823)

Specialists

It has been only a few years since the old-time general practitioner was everywhere. Just look around you and see now how the system has changed! If your liver begins to misconduct itself the first thought of the modern operator is to cut it out and hide it some place where you can't find it. The old-timer would have bombarded it with a large brunette pill about the size and color of a damson plum.

Except in the country the old-time, catch-as-catch-can general practitioner appears to be dying out. Hence the expert who treats you for just one particular thing. With a pain in your chest, say, you go to a chest specialist. So long as he can keep the trouble confined to your chest, all well and good. If it slips down or slides up he tries to coax it back to the reservation. If it refuses to do so, he bids it an affectionate adieu, makes a dotted mark on you to show where he left off, collects his bill and regretfully turns you over to a stomach specialist or a throat specialist, depending on the direction in which the trouble was headed when last seen.

— Irvin S. Cobb: Speaking of Operations

Medical Men on Postage Stamps

Aesculapius, Thessalonian physician immortalized as the god of medicine, has been commemorated on a postage stamp by two countries: Romania in 1932 and Spain in 1948.

Agostini Bassi (1773-1856), microbiologist and precursor of Pasteur and Koch, advocate of the germ theory of disease, and author of works on pellagra and cholera, was honored on an Italian postage stamp in 1953.

Medical Economics

Is Your Home a Sound Investment?

If someone were to tell you that the difference in cost between a $35,000 residence and a $70,000 residence can amount to $130,000 you would be inclined to think that he had completely lost his wits. However, it is true!

For the past several years we have noted an ever-increasing trend toward bigger, more costly homes — far too frequently at the expense of a sound over-all financial plan. Just how much "status symbolism" is involved in these ultra-expensive homes is not known; but it is immediately obvious that they involve some objective beyond adequate housing.

Too frequently the size of the investment in a residence is governed by the monthly mortgage payments. If the payment can be supported, the cost is often disregarded or considered inconsequential. Rarely does the prospective buyer measure the true and complete cost of a luxury-house in comparison to an adequate home.

In an effort to measure this cost, we recently studied the financial aspects of owning homes at various price levels. In the following example we have assumed that our client is in a 40% top tax bracket and is considering the purchase of one of three homes — one costing $35,000, one costing $50,000, and one costing $70,000. He has $15,000 cash for equity.

	House A	House B	House C
Total Cost	$35,000	$50,000	$70,000
Cash for Equity	15,000	15,000	15,000
Mortgage Balance	$20,000	$35,000	$55,000
Monthly Mortgage Payment (20 year, 6% mortgage)	$143.29	$250.76	$394.10

At this point, the Doctor feels he can support the $394.10 monthly payment but wonders what other factors may be involved:

Estimated Annual Difference	House B Over House A	House C Over House A
Annual Mortgage Payment	+ $1,300	+ $3,000
Additional Property Taxes	+ 400	+ 1,200
Additional Maintenance	+ 100	+ 500
Estimated Annual Difference — 20 Years	+ $1,800	+ $4,700

Here we discover that House B will require about $150 per month in cash outlay over House A; House C will require nearly $400 more per month. These differences do not even consider additional and more expensive furniture, additional domestic help and the inevitable increase in the over-all cost of living which accompanies the luxury home.

The Doctor is impressed at this point — but our comparison has only begun. What would this monthly difference amount to if invested wisely in a productive medium?

In House B, the cost differential was $1,800 per year; however, this includes interest and taxes which are deductible and result in tax savings. The after-tax difference is $1,425 per year. If this amount were invested to yield and appreciate at 6%, the net after-tax performance would be about 3½% and this would accumulate to $43,500 over the twenty-year mortgage period.

In House C, the cost differential was $4,700 before tax, or $3,700 after tax. This invested under the same circumstances as previously stated would grow to $100,000 over the twenty-year period.

Continued

If we were to make a very liberal assumption that these homes would retain their original cost differential, the loss from purchasing House B over House A would be $43,500 less $15,000, cost differential, or a net loss of $28,500. The loss on House C would be $104,000 less $35,000, cost differential, or a net loss of $69,000.

Extending the period of ownership from twenty years to thirty years would increase the net loss on House B to about $50,000 and the net loss on House C to about $130,000. These figures give dramatic emphasis to our contention that excessive expenditure on a residence can have permanent and serious results in terms of accomplishing a reasonable degree of financial security. These figures also point out the logic of measuring the long-term effect of an excessive residential commitment — as compared to the trend toward measuring the size of the commitment in terms of ability to meet the monthly mortgage payment.

While there are advocates of various "rules of thumb" for measuring the amount which should be invested in a home, we believe that this determination can be made on the basis of a study of the individual's specific financial circumstances. For example, a Doctor earning $30,000 might have debt and family circumstances which should limit his home cost to $25,000, while another earning $30,000, having just inherited $100,000, could reasonably spend $50,000.

In the absence of unusually favorable circumstances, such as sizeable inheritance or outstanding past investment success, or various adverse circumstances, such as bad health or heavy liabilities, the following guide is probably reasonable for the average Doctor.

Annual Income Before Taxes	Reasonable Value for Residence	Maximum Mortgage
$ 20,000	$25,000	$20,000
30,000	30,000	20,000
40,000	35,000	25,000
50,000	40,000	25,000
60,000	45,000	25,000
70,000	50,000	30,000
80,000	55,000	30,000
90,000	60,000	30,000
150,000	75,000	35,000

In addition to the value of the residence, the matter of maximum mortgage is quite important. The further you advance into luxury-type homes, the greater the ratio of equity to debt should be. This is based upon our philosophy of purchasing luxuries with previously accumulated funds rather than purchasing them with future earnings. Following this guide for total cost and maximum mortgage will also insure an adequate residue of funds for use in accumulating income-producing assets.

In summary, it has been our experience that over-commitment for a residence can cause more financial problems than any other single phase of your financial planning. In considering a residence purchase, all factors must be considered objectively and the final decision must be based upon financial logic rather than pure desire. Once a final decision has been made, you are going to have to live with it for many years.

William D. Huntington*
Minneapolis, Minnesota

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*Northern Division Manager, Professional Management Midwest.

MINNESOTA MEDICINE Cover Photographs

In order to encourage more physicians to submit color slides for use on the cover of MINNESOTA MEDICINE the competition is being discontinued. The picture editor now invites all physician-photographers to send 35 mm. color slides of suitable subjects for consideration as cover pictures. The format must be horizontal because of printing limitations. Pictures highlighting Minnesota seasons, places, and activities will have an automatic advantage. No limit as to the number of slides sent will be set, but all slides should be individually identified. All slides will be returned. Physicians whose pictures are used as covers will be recognized in MINNESOTA MEDICINE. We can use many more pictures than we have received in the past.

Meetings and Announcements

Appreciation, whether of nature, or books, or art, or men, depends very much on temperament. What is beauty or genius or greatness to one, is far from being so to another. — Tyrone Edwards

JANUARY

Southwestern Minnesota Medical Society — January 2, Worthington, 7 p.m.

Zumbro Valley Medical Society — January 4, Mann Hall, Rochester, 8:00 p.m.

Brown County Medical Society — January 10, Orchid Inn, Sleepy Eye, 7:00 p.m.

Minnesota Academy of Medicine — January 11, Town & Country Club, St. Paul, 6:30 p.m.

Camp Release District Medical Society — January 12, Hunt Hotel, Montevideo, 6:30 p.m.

St. Louis County Medical Society — January 12, Ex. Comm. at 6:00 p.m.; annual business meeting at 8:00 p.m., St. Mary's Hospital, Duluth.

Blue Earth Valley Medical Society — January 18, Interlaken Golf Club, Fairmont.

Twin City Urological Society — January 20, 6:00 p.m.

Range Medical Society — January 24, Ex. Comm. & annual meeting; 7:00 p.m. dinner, meeting follows, Hibbing.

National Winter Sports Injury Conference — January 27-29, University of Wisconsin Medical School, Wisconsin Center, Madison, Wisconsin.

Ramsey County Medical Society — 8:00 p.m. — January 30, 15th floor, Lowry Medical Arts Bldg., St. Paul.

Big Mountain Medical-Ski Conference, Whitefish, Montana, January 25, 26, 27. Contact: R. D. Buchanan, M.D., Box 220, Columbia Falls, Montana. AAGP Credit 6½ hours. Registration fee: $5.00.

FEBRUARY

Southwestern Minnesota Medical Society — February 6, Worthington, 7:00 p.m.

Nicollet-LeSueur County Medical Society — February 6, Holiday House, St. Peter, 6:30 p.m.

Scott-Carver County Medical Society — February 7.

St. Louis Co. Med. Society — St. Lukes, Duluth — February 9, (Ex. Comm. at 6:00 p.m. Regular meeting at 8.)

Minnesota Academy of Medicine — February 8, Town & Country Club, St. Paul, 6:30 p.m.

Camp Release District Medical Society — February 10, Hunt Hotel, Montevideo.

Wisconsin Academy of General Practice — February 14-16, Mt. Telemark Ski Conference, Cable, Wisconsin.

Blue Earth Valley Medical Society — February 15, Interlaken Golf Club, Fairmont.

Minnesota Academy of Occupational Medicine and Surgery — February 16, Minneapolis Club, 6:30 p.m.

Twin City Urological Society — February 17, 6:00 p.m.

Hennepin County Academy of General Practice — February 20, Athletic Club, Minneapolis, 6:00 p.m.

Ramsey County Medical Society — February 27, 15th floor, Lowry Medical Arts Bldg., St. Paul, 8:00 p.m.

Announcement

A combined meeting of the Minneapolis Surgical Society and the Hennepin County Medical Society will be held January 9 at the Pick-Nicollet Hotel, 6:00 p.m. Inaugural Theses: Eugene F. Bernstein, M.D. "Long Term Results in the Treatment of Abdominal Aortic Aneurysms"; Richard E. Larson, M.D. "Obstructive Lesions of the Superior Mesenteric Artery."

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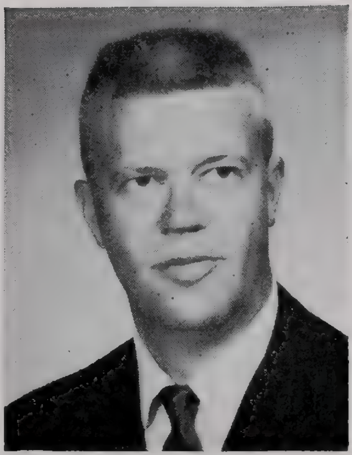
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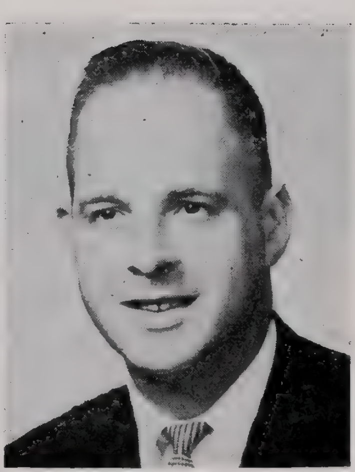
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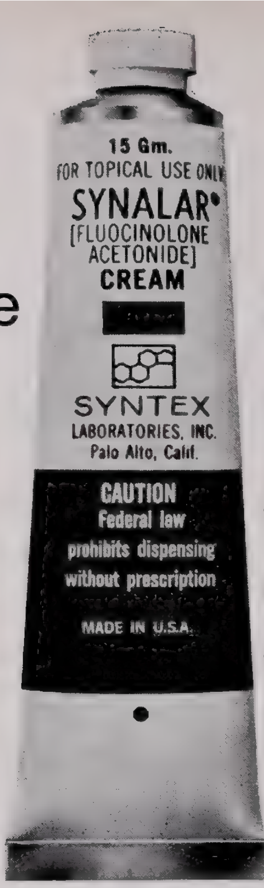

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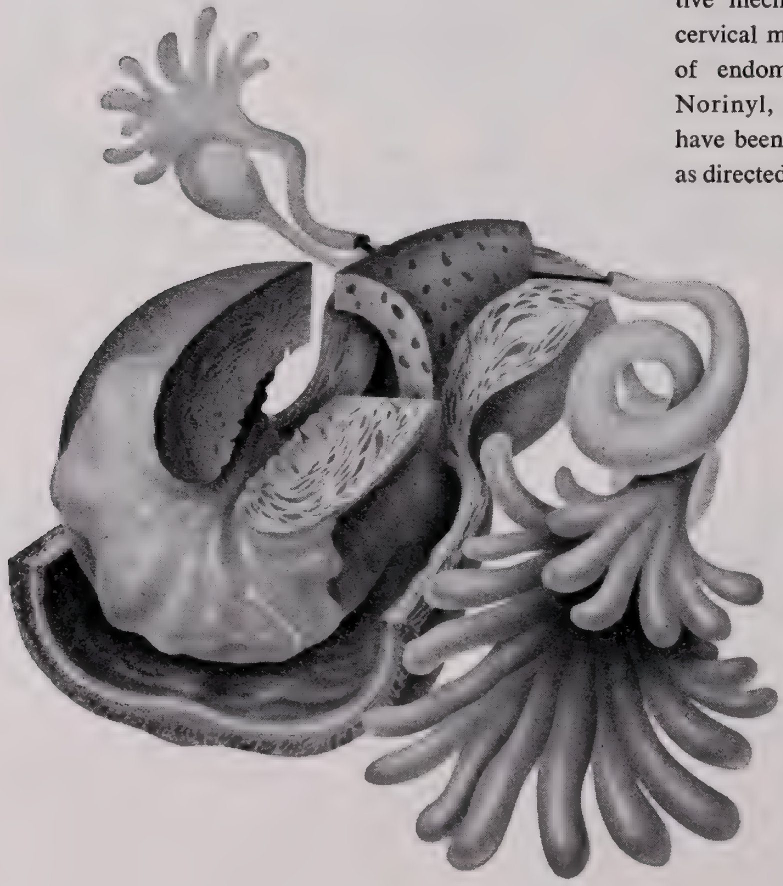

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Warning: Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Precautions: By May 1963, experience with norethindrone 2 mg.—mestranol 0.1 mg. had extended over 24 months. Through miscalculation, omission or error in taking the recommended dosage of Norinyl, pregnancy may result. If regular menses fail to appear and treatment schedule has not been adhered to, or if patient misses two menstrual periods, possibility of pregnancy should be resolved before resuming Norinyl. If pregnancy is established, Norinyl should be discontinued during period of gestation since virilization of the female fetus has been reported with oral use of progestational agents or estrogen. When lactation is desired, withhold Norinyl until nursing needs are established. Existing uterine fibroids may increase in size. In metabolic or endocrine disorders, careful clinical preevaluation is indicated. A few patients without evidence of hyperthyroidism had elevated serum protein-bound iodine levels, which in the light of present knowledge, does not necessarily imply hyperthyroidism. Protein-bound iodine increased following estrogen administration. Bromsulphalein retention has occurred in up to 25% of patients without evidence of hepatic dysfunction. Studies from 24-hour urine collections have shown an increase in aldosterone and 17-ketosteroids and decrease in 17-hydroxycorticoid levels. Thus, Norinyl should be discontinued prior to and during thyroid, liver or adrenal function tests. Because progestational agents may cause fluid retention, conditions such as epilepsy, migraine and asthma require careful observation. Thus far no deleterious effect on pituitary, ovarian or adrenal function has been noted; however, long-range possible effect on these and other organs must await more prolonged observation. Norinyl should be used with caution in patients with bone, renal or any disease involving calcium or phosphorus metabolism.

Side Effects: Intermenstrual bleeding; amenorrhea; symptoms resembling early pregnancy, such as nausea, breast engorgement or enlargement, chloasma and minor degree of fluid retention (if these should occur and patient has not strictly adhered to medication plan, she should be tested for pregnancy); weight gain; subjective complaints such as headache, dizziness, nervousness, irritability; in a few patients libido was increased. In a total of 3,090 patients, 2.2% discontinued medication because of nausea.

NOTE: See sections on contraindications and precautions for possible side effects on other organ systems.

Dosage and Administration: One Norinyl tablet orally for 20 days, commencing on day 5 through and including day 24 of the menstrual cycle. (Day 1 is the first day of menstrual bleeding.)

Availability: Dispensers of 20 and 60 tablets; bottles of 100.

References: **1.** Council on Drugs. JAMA 187:664 (Feb. 29) 1964. **2.** Brvans, F. E.: Canad Med Ass J 92:287 (Feb. 6) 1965. **3.** Goldzieher, J. W.: Med Clin N Amer 48:529 (Mar.) 1964. **4.** Cohen, M. R.: Paper presented at Symposium on Low-Dosage Oral Contraception, Palo Alto, Calif., July 15, 1965. Reported in Med Sci 16:26 (Nov.) 1965. **5.** Hammond, D. O.: Ibid. **6.** Rice-Wray, E., Goldzieher, J. W., and Aranda-Rosell, A.: Fertil Steril 14:402 (Jul.-Aug.) 1963. **7.** Goldzieher, J. W., Moses, L. E., and Ellis, L. T.: JAMA 180:359 (May 5) 1962. **8.** Kempers, R. D.: GP 29:88 (Jan.) 1964. **9.** Tyler, E. T.: JAMA 187:562 (Feb. 22) 1964. **10.** Rudel, H. W., Martinez-Manautou, J., and Maqueo-Topete, M.: Fertil Steril 16:158 (Mar.-Apr.) 1965. **11.** Flowers, C. E., Jr.: N Carolina Med J 25:139 (Apr.) 1964. **12.** Goldzieher, J. W.: Appl Ther 6:503 (June) 1964. **13.** The Control of Fertility. Report adopted by the Committee on Human Reproduction of the American Medical Association. JAMA 194:462 (Oct. 25) 1965. **14.** Flowers, C. E., Jr.: JAMA 188:1115 (June 29) 1964. **15.** Merritt, R. I.: Appl Ther 6:427 (May) 1964. **16.** Newland, D. O.: Paper presented at Symposium on Low-Dosage Oral Contraception, Palo Alto, Calif., July 15, 1965. Reported in Med Sci 16:26 (Nov.) 1965.

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1. McCabe, W. R., and Jackson, G. G.: New England J. Med. 272:1037, 1965.

in gram-negative urinary tract infections often the single well-chosen agent

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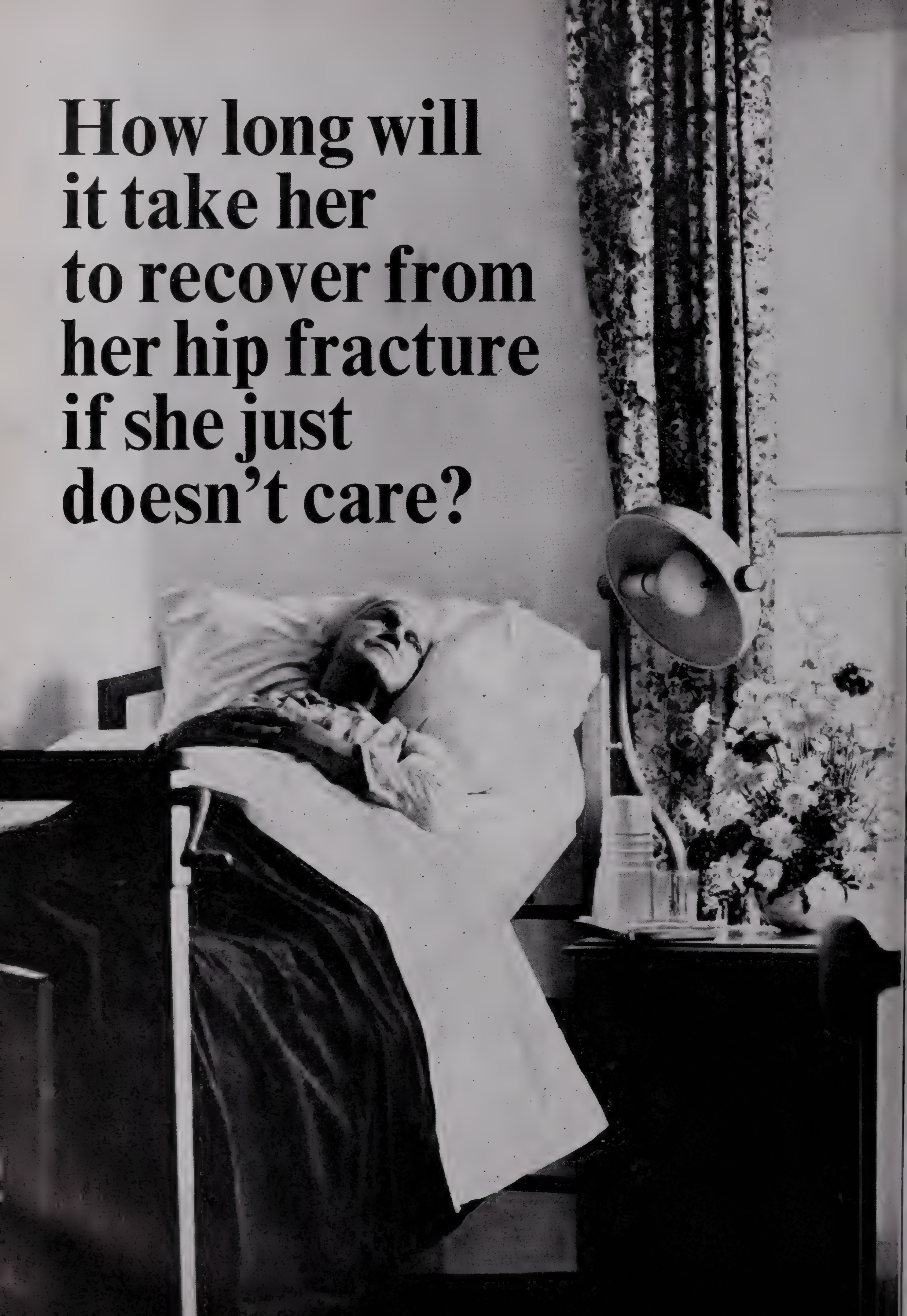
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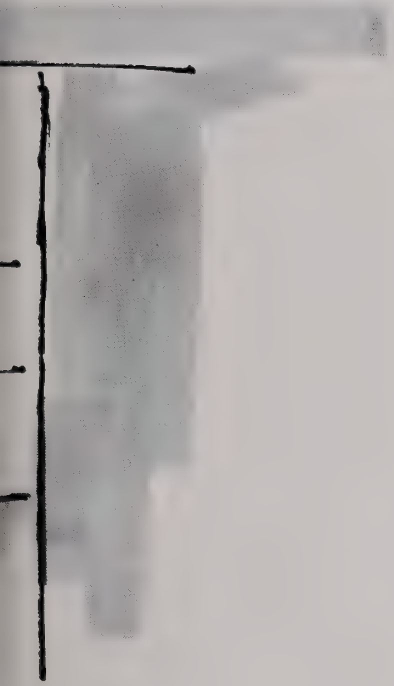

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Tribute from a Scholar

Whilst I allow, that peculiar and important advantages arise from the appropriate studies of the three learned professions, I must confess, that in erudition, in science, and in habits of deep and comprehensive thinking, the pre-eminence must be assigned, in some degree, to physicians.

The most desirable profession is that of medicine; the practice of law spoils a man's moral sense and philosophic spirit; the Church is too bigoted and stiff-starched; but the study and practice of physic are equally favorable to a man's moral sentiments and intellectual faculties.

— Samuel Parr (1747-1825)

Thirtieth Annual Meeting
The New Orleans Graduate Medical Assembly

The thirtieth annual meeting of The New Orleans Graduate Medical Assembly will be held March 6, 7, 8, 9, 1967, headquarters at The Roosevelt Hotel.

Nineteen outstanding guest speakers will participate and their presentations will be of interest to both specialists and general practitioners. The program will include fifty-one informative discussions on many topics of current medical interest, in addition to clinicopathologic conferences, symposia, medical motion pictures, round-table luncheons and technical exhibits. This program is acceptable for thirty and one-half (30½) accredited hours by the American Academy of General Practice.

An interesting and enjoyable program of entertainment for visiting ladies has been planned.

For information concerning the Assembly meeting write Secretary, The New Orleans Graduate Medical Assembly, 1430 Tulane Avenue, Room 1528, New Orleans, Louisiana 70112.

Old Medical Equipment Needed

Minneapolis People to People are sponsoring a drive for used or repairable medical equipment and supplies which will be sent to Santiago, Chile, the Sister City of Minneapolis.

Doctors are asked to bring the material to the hospitals, which are serving as collection points. If the equipment is too large to be transported, please call Joe Paulson of the Jaycees at Swedish Hospital X-Ray department (333-4171) in Minneapolis.

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January 2 — *Chromosome Studies — Why and When*
Dr. Campbell Moses, Moderator
Dr. Niel Wald, Radiologist, Pittsburgh

January 9 — *Common Chromosomal Disorders*
Dr. Wayne Zundel, Moderator
Dr. Frank Tyler, Internist, Utah
Dr. Marvin L. Rallison, Pediatrician, Utah
Dr. William MacDiarmid, Internist, Utah

January 16 — *Practical Aspects of Psychiatry for the Physician*
Dr. Albert Sullivan, Moderator
Dr. George Williams, Psychiatrist, Minnesota

January 23 — *Arteriosclerosis — Fact and Fancy*
Dr. Campbell Moses, Internist, Pittsburgh

January 30 — *Multiple Sclerosis*
Dr. Campbell Moses, Moderator, Pittsburgh
Dr. James A. Rosen, Neurologist, Pittsburgh

Physician's Diary

If a civil word or two will render a man happy, he must be a wretch, indeed, who will not give them to him. Such a disposition is like lighting another man's candle by one's own, which loses none of its brilliancy by what the other gains. — Penn

The University of Minnesota has announced a new medical research project on the role of gastric and intestinal secretions in the regulation of iron absorption which will start at the University of Minnesota's College of Medical Sciences under the direction of **Dr. M. John Murray**, associate professor of medicine.

* * *

Dr. Bror F. Pearson, Shakopee physician, has volunteered under the AMA Volunteer Physicians for Vietnam program for a 60-day period of service in South Vietnamese civilian hospitals. He will leave for Vietnam in October.

* * *

Dr. M. J. Lindahl of Sherburn was recently featured on the cover of the August issue of the Assembly of God Church Magazine, "Team."

* * *

Dr. Laurentius O. Underdahl became president of the American Diabetes Association at its annual meeting in Chicago. Dr. Underdahl is associate professor of clinical medicine at the Mayo Graduate School of Medicine and head of a medical section at the Mayo Clinic.

* * *

Dr. L. R. Lima of Montevideo has been elected to active membership in the American Academy of General Practice, and **Dr. John E. Mathers** of Austin has been elected to membership in the American Board of Obstetrics and Gynecology.

* * *

Dr. Edith Parkhill, pathologist at the Mayo Clinic, retired from the Clinic in September. She will continue to live in Rochester.

* * *

Dr. Richard M. Magraw, University of Minnesota professor of psychiatry and medicine and director of the University's comprehensive clinic, received the 1966 Norman A. Welch, M.D., Memorial Award, for his book, "Ferment in Medicine." In presentation of the award it was noted that the judges felt, without dissent, that Dr. Magraw's book represented "the most scholarly and meritorious contribution to the literature of medical (care)" during the past year.

* * *

The following surgeons were inducted as new Fellows of the American College of Surgeons during its five-day Clinical Congress in San Francisco in October: **Dr. John L. Sander** of Cambridge, **Dr. Owen W. Holm** of Crookston, **Doctors Anderson C. Hilding, Don P. Swensen** and **John V. Thomas** of Duluth, **Doctors Clyde E. Blackard, Arndt J. Duvall III, Henry Gans, Stanley M. Goldberg** and **Howard M. Levine** of Minneapolis, **Doctors Lowell F. A. Peterson, Jack L. Pulec, Robert B. Wallace,** and **Tiffany J. Williams** of Rochester, **Doctors Frank T. Brown** and **Carl B. Thuringer** of St. Cloud, **Doctors John B. Brainard** and **Thomas L. Huseby** of St. Paul and **Dr. David E. Martin III** of Wabasha.

* * *

Dr. Russell L. Drake, head of the Section of Medical Illustration of the Mayo Clinic from 1932 to 1961, was awarded a special citation and certificate in honor of his contributions to the Association of Medical Illustrators at the 21st annual meeting of the organization in Atlanta, Georgia, in October.

* * *

Dr. C. Allen Good, head of the Section of Roentgenology of the Mayo Clinic, Rochester, and professor of radiology in the Mayo Graduate School of Medicine, was chosen president-elect of the American Roentgen Ray Society at its annual meeting at San Francisco in September.

* * *

Dr. E. Larry Kruger of Nashwauk was recently honored by that community on occasion of his tenth year anniversary as Nashwauk's physician.

* * *

Dr. Robert R. Kierland, head of the Section of Dermatology of the Mayo Clinic, was elected chairman of the Section on Dermatology of the American Medical Association at the 115th annual session of the organization in June.

Who'd hire mentally retarded people?

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Whether you're the head of a big business like W. T. Grant Company or a small one like Youngblood's Fried Chicken Restaurant, you'd be smart to hire mentally retarded people. For they actually do some jobs better than people of average intelligence.

That's because they don't get bored by repetition or routine. They like to load trucks, tighten bolts on assembly line jobs, trim hedges, sort and deliver mail.

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Right now, over two million mentally retarded people are employed by private companies and government agencies in many different kinds of jobs. They've worked out so well, many people are hiring more.

Think it over. And write for a free booklet to The President's Committee on Mental Retardation, Washington, D.C.

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Minnesota Medicine at a Glance

Nerves to the Esophageal Hiatus — Wynyard & Kletschka Page 1821

A better understanding of the esophageal hiatus and its nerve supply might provide a better end result in the surgical repair of this relatively common defect.

The authors have indicated that injury to the terminal branches of the crural nerves can occur when the defect in the hiatus is closed posteriorly, because this is the position in which the nerves course in the musculature forming the crura. It has been shown that when these nerves are crushed, a corresponding area of the diaphragm undergoes atrophy.

Subcutaneous Injuries — Stark and Connelly Page 1825

It is not always necessary in injury that the skin be broken, and as Stark and Connelly have indicated in their case reports, the subcutaneous fat may be separated from the underlying fascia and the overlying skin, resulting in the accumulation of serosanguineous exudate or other tissue material, which in turn provides delay in healing and other associated complications.

They emphasize the importance of early recognition and prompt treatment in order to reduce the morbidity from this type of injury.

Tomography of the Respiratory Tract — Heitzman et al. Page 1829

The polytome makes it possible to visualize the pulmonary tract from many different angles. In the use of this machine the hypocycloidal motion above and below the plane of interest results in grayness of the surrounding tissue, but makes it possible to visualize a small lesion more clearly. After the lesion has been localized, then a thin hypocycloidal section can be made for detailed analysis.

These observations are illustrated in the accompanying photographs.

Acute Arterial Occlusion — Gregg Page 1835

The authors have presented their views regarding the proper management of acute arterial occlusion and have pointed out the importance of differentiating between acute venous thrombosis and acute arterial occlusion, stressing also the importance of evaluating the entire cardiovascular system so as to determine how much a poor cardiac output affects peripheral ischemia.

They also endeavor to determine the patient's ability to withstand surgery and anesthesia so as to be able to project how well his heart will function in the future if an operation is to be undertaken on the affected extremity.

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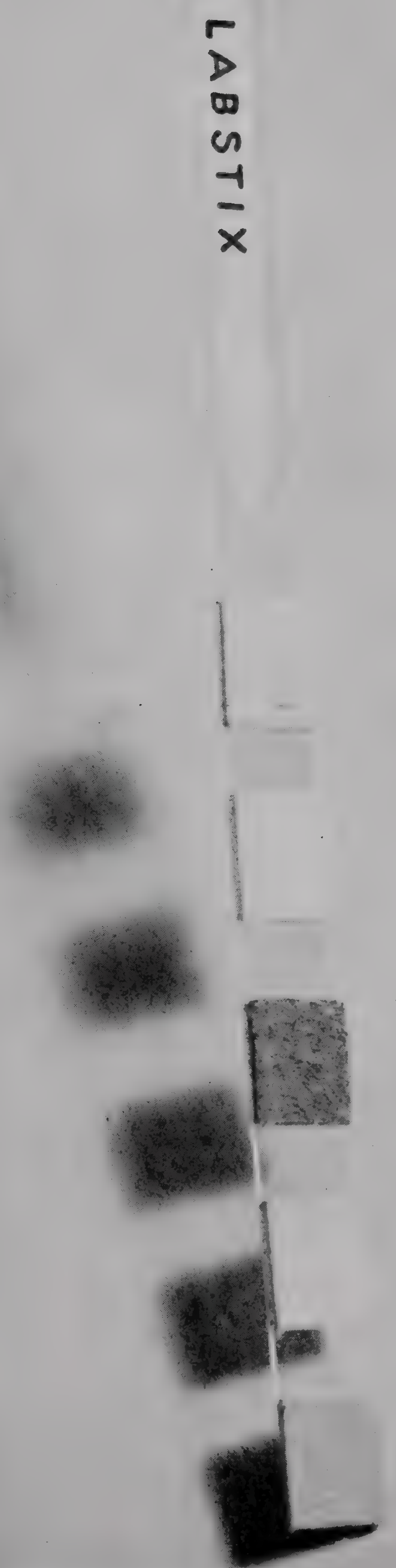

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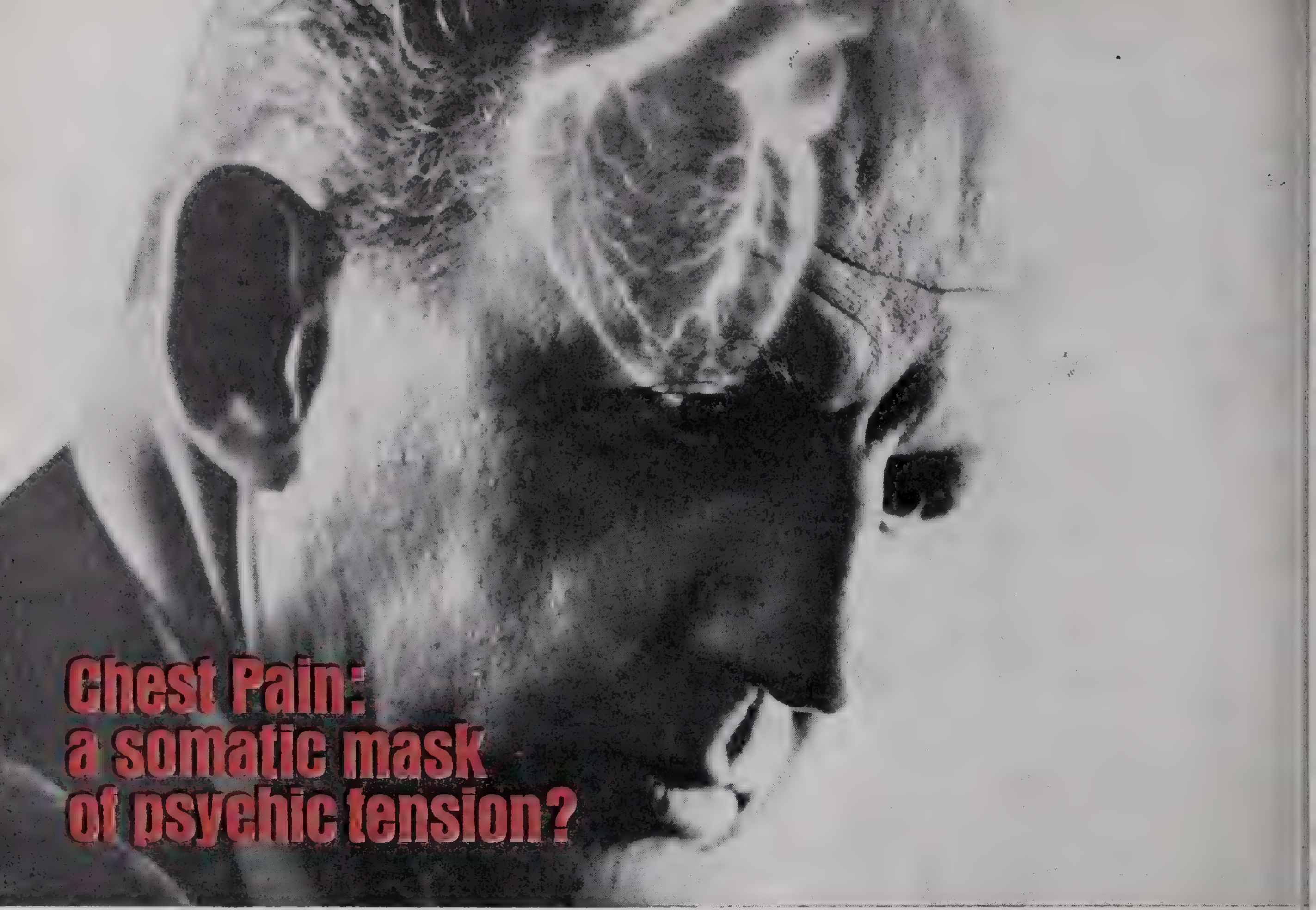

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